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Meta-analysis and multidimensional data investigation of the cardiovascular effects and processes of Phyllanthus emblica and its functional components

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ABSTRACT: Background: Phyllanthus emblica and its active constituents appear to enhance cardiovascular function, according to research on cardiovascular-related problems. Thus, this paper's objectives are to examine the cardiovascular effects of consuming Phyllanthus emblica and its functional constituents, to investigate possible mechanisms of action, and to offer safety data for individualized nutritional interventions and the use of functional foods derived from Phyllanthus emblica in middle-aged and elderly patients with cardiovascular disease and possible pathogenicity. **Methods:** The terms "Phyllanthus emblica" and "cardiovascular disease" were searched in Pubmeb, Embase, Web of Science, and the Cochrane Library, and a meta-analysis of the evidence supporting links between the two was carried out. The search was conducted from its inception to 31 December 2024. Included were randomized controlled trials (RCTs) that looked into Phyllanthus emblica or its active ingredients consumption. Online databases were used to check for genes linked to cardiovascular disease. The possible mechanisms for Phyllanthus emblica ameliorating cardiovascular disease were investigated using Mendelian randomization, genomic enrichment analysis, machine learning, and molecular docking. **Results:** A total of 725 articles were retrieved and 6 articles were finally included in this study, all of which were randomized controlled trials with a total of 397 subjects. The results of meta-analysis showed that there was a statistical difference between the experimental group and the control group in terms of lipid-related indicators [TG:OR=0.69,95%CI=(-0.00,1.38), $P < 0.05$;TC:OR=0.69,95%CI=(0.23,1.14), $P < 0.05$; LDL:OR=0.93,95%CI=(0.23,1.63), $P < 0.05$;HDL:OR=-0.80,95%CI=(-1.59,-0.02), $P < 0.05$; VLDL:OR=0.39,95%CI=(-0.01,0.78), $P < 0.05$] as well as other cardiovascular-related indicators[NO:OR=-2.31,95%CI=(-3.86,-0.95), $P < 0.05$; GSH:OR=-2.20,95%CI=(-4.15,-0.26), $P < 0.05$; MDA:OR=1.25,95%CI=(-0.03,2.53), $P < 0.05$;hsCRP:OR=1.36,95%CI=(0.12,2.60), $P < 0.05$].Seven key effector genes associated with cardiovascular disease were identified based on network pharmacology and machine learning algorithms: AKT1, ABCB1, FYN, IGF1R, NR3C1, PIK3CA, and SYK. Mendelian randomization was also validated to find a causal relationship between AKT1, FYN, IGF1R, and SYK and cardiovascular disease. **Conclusion:** Phyllanthus emblica and its functional constituents have significant effects on cardiovascular disease, and the mechanisms may involve the involvement of AKT1, ABCB1, FYN, IGF1R, NR3C1, PIK3CA and SYK, as well as the regulation of metabolic and immune-related pathways.

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1. Introduction

Cardiovascular disease (CVD) is the leading cause of death and disability worldwide[1]. According to data from the World Health Organization, it is predicted to result in 19.91 million deaths in 2021. With the intensification of population aging, the burden of CVD worldwide will continue to increase, especially among middle-aged and older adults. Acute myocardial infarction, cardiac failure, atrial fibrillation, and atherosclerosis are examples of common CVDs[2]. Patients typically experience dizziness, palpitations, dyspnea, and chest pain or tightness. There are many risk factors for CVD, such as obesity, smoking, elevated cholesterol, diabetes, hypertension, sedentary lifestyle, and unhealthy eating habits[3]. Although there are many other approaches to treating CVD, the three mainstays are medication, surgery, and intervention. However, due to the high morbidity and mortality of CVD, there is a great need for effective and cost-effective therapies to reduce the risk of CVD[4].

Phyllanthus emblica is a plant of the genus Phyllanthus, widely distributed in most tropical and subtropical countries, and all its parts, including its fruits, flowers, seeds, leaves, and bark, have been widely used in many traditional therapies[5]. Phyllanthus emblica has been demonstrated in numerous studies to have anti-inflammatory[6], anti-cancer[7], gastrointestinal[8], blood sugar[9], anti-ageing[10], halitosis[11], and immune-modulating[12]properties.In addition to being high in protein, fibre, and carbohydrates, Phyllanthus emblica is also a good source of calcium, phosphorus, and iron[13,14]. Polyphenols, polysaccharides, flavonoids, organic acids, saponins, terpenoids, tannins, phenolic acids, and other compounds are the main functional constituents of Phyllanthus emblica. Many of these compounds have anti-inflammatory and anti-aging properties and have been used to formulate herbal and patent medicines, as well as to treat cancer, diabetes, liver disease, heart disease, and anaemia[5].

Despite this, some reports indicate that Phyllanthus emblica might help treat heart conditions. Nonetheless, there is still limited and regionally restricted research in these interconnected fields. Most research has been done primarily from a theoretical or clinical standpoint, with little attention to mechanisms. Consequently, a thorough investigation of the molecular mechanisms and material foundation of the connection between Phyllanthus emblica and CVD is required. This paper integrates the findings of earlier research, utilizing a meta-analysis to reflect the current state of the field. To identify the active ingredients and clarify the overall mechanism, the molecular association pattern between Phyllanthus emblica and CVD was examined using network pharmacology from both a systemic and comprehensive biological network perspective [15]. In addition, bioinformatics analyses, transcriptomic datasets, and multiple databases were used to identify and assess core gene targets of Phyllanthus emblica associated with CVD. Molecular docking and gene function enrichment analyses were performed to explore the inter-binding roles and potential mechanisms of the functional components of Phyllanthus emblica in relation to the core genes. Finally, the causal relationship between core genes and CVD was explored using Mendelian randomisation. This study

aimed to elucidate the effects of Phyllanthus emblica and its functional components on CVD and to provide safety recommendations for its application in food and drugs.

2. Information and Methods

2.1 Study Design and Workflow

This study was designed to comprehensively investigate the therapeutic effects of Phyllanthus emblica on CVD and to elucidate its underlying mechanisms through an integrated analytical approach, consisting of three components (Figure 1).

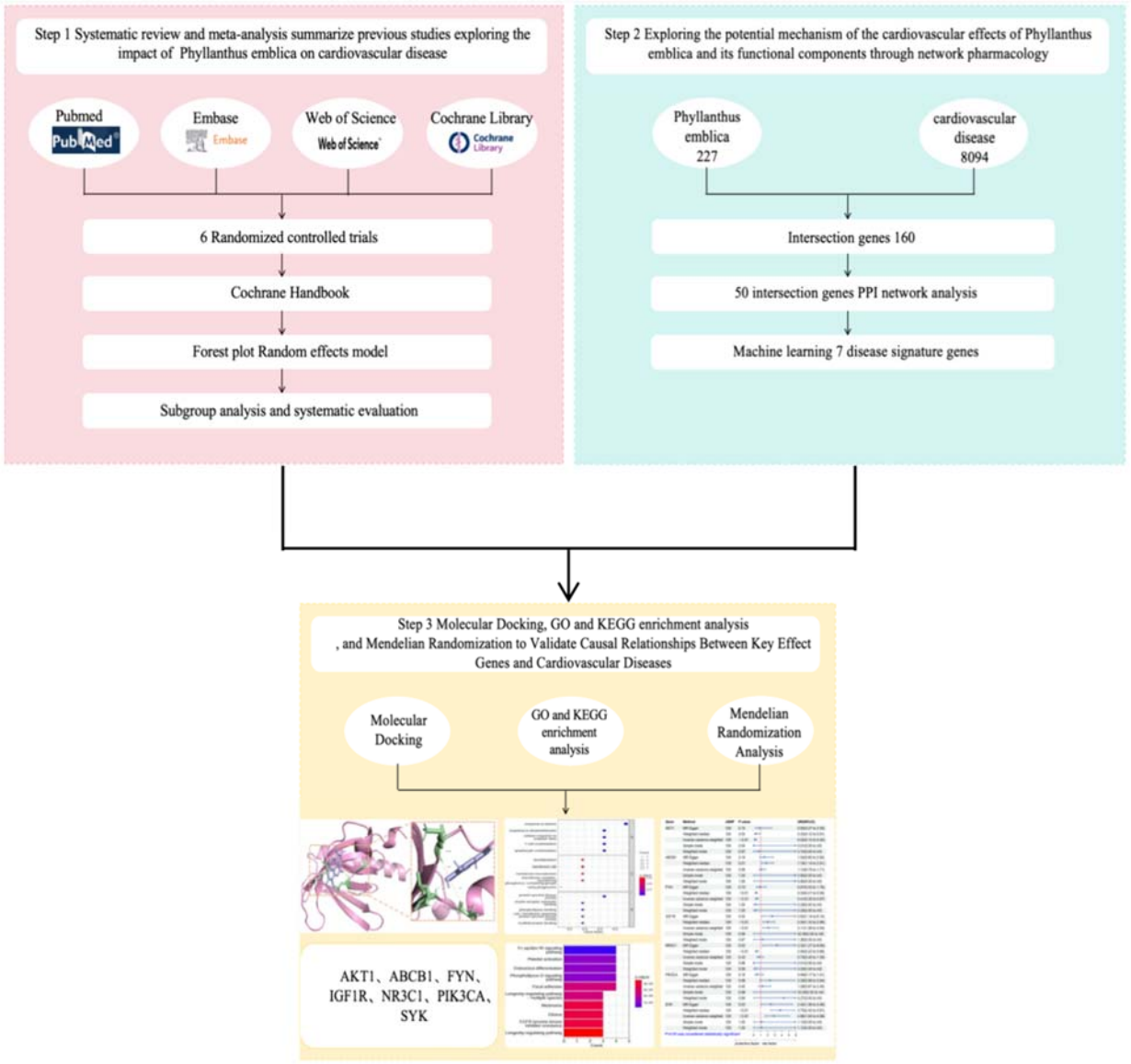


Figure 1. Schematic illustration of the overall study design.

First, a systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted. A comprehensive literature search was performed across multiple electronic databases. Following an abstract-based screening process, six studies met the inclusion criteria. The risk of bias and publication bias in the included studies were assessed using RevMan, while quantitative synthesis was performed using Stata.

Subsequently, CVD-related genes and biomarkers were identified. Candidate genes were sourced from the OMIM and GeneCards databases, supplemented by transcriptomic data. The intersection of these genes

was analyzed, and machine learning algorithms were employed to refine and identify robust biomarkers for CVD.

Finally, based on the findings from the meta-analysis, the potential mechanisms through which Phyllanthus emblica confers cardiovascular benefits were explored. An integrated strategy combining toxicological prediction, molecular docking, and Mendelian randomization analysis was applied to investigate the interactions and causal relationships at the molecular level.

2.2 Literature selection

2.2.1 Inclusion criteria

(1) Type of literature study: The literature gathered consisted of publicly available publications from randomized controlled trials on the relationship between Phyllanthus emblica and cardiovascular function.

(2) Study subjects: patients with CVD or symptoms of related CVD and those with potential morbidity.

(3) The timeframe for the literature study is from its inception to December 31, 2024.

(4) Clear sample size and literature sources.

(5) Intervention: All intervention groups were treated with Phyllanthus emblica or its functional ingredient products, while the control group received a placebo.

2.2.2 Exclusion criteria

(1) Baseline information is not comparable between the intervention and control groups.

(2) Data sources in the literature are incomplete or unavailable.

(3) The random grouping method is not justified.

(4) The intervention and control groups are non-parallel controls.

(5) Non-strictly randomized controlled studies, case studies, non-human subjects, etc.

(6) Taking other cardiovascular medications at the same time.

2.3 Search Strategies

This systematic review and meta-analysis is registered with PROSPERO (registration number: CRD420251019924). Search keywords included Phyllanthus emblica and cardiovascular disease. Search terms for Phyllanthus emblica and (cardiovascular disease, coronary heart disease, heart failure, arrhythmia, hypertension, or atherosclerosis). Databases searched included PubMed, The Cochrane Library, Embase, and Web of Science for the period commencing until 31 December 2024. The literature searched was RCTs on Phyllanthus emblica and CVD.

2.4 Literature screening and data extraction

Two researchers conducted independent literature screening and data extraction, and then cross-checked their findings against the inclusion and exclusion criteria described above. For the literature that could not be excluded or included after reading the abstract, further review of the full text led to the drawing of conclusions. When two researchers disagreed on the inclusion and exclusion of literature, a third researcher assisted in resolving the issue. Literature screening was conducted by first reviewing the text headings and then, after

excluding irrelevant literature, further reading the abstract and full text to determine inclusion. Basic information extracted from the literature included the name of the first author, country of study, year of publication, sample size of experimental and control groups, patient age, gender composition, duration of treatment, and outcome indicators.

2.5 Quality evaluation

The literature quality assessment was conducted independently and cross-checked by two researchers. The quality of the included literature was assessed using the Modified Jadad Scale and the Cochrane Collaboration tool[16]. The modified Jadad scale was proposed by Greenhalgh[17] and Oremus[18], where scores ranging from 1 to 3 are classified as low-quality literature, and scores ranging from 4 to 7 are classified as high-quality literature. (Figure S1, Table S1).

2.6 Selection of efficacy indicators

The primary indicators of Phyllanthus emblica therapy are lipid-related, and secondary indicators are other physiological and biochemical indicators of cardiovascular relevance.

2.7 PICO standards

Eligible Population, Intervention, Comparison, and Outcome (PICO) characteristics[19] were (1) Population: patients with a particular CVD or with associated CVD symptoms. (2) Interventions: all interventions were treated with Phyllanthus emblica or its functional components. (3) Comparison: all controls were treated with a placebo. (4) Outcome: The outcome indicators are lipid-related.

2.8 Cyberpharmacology to explore the potential mechanisms of cardiovascular effects of Phyllanthus emblica and its functional components

2.8.1 Identification of drug target genes

Eighteen components of Phyllanthus emblica were obtained from the Traditional Chinese Medicine Systematic Pharmacology Database and Profiling Platform (TCMSP) with filtering criteria of oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18. The SwissADME database was used to screen five further functional constituents, namely ellagic acid, luteolin, Phyllanthin, kaempferol, and quercetin, using the filter criteria of 'high' oral bioavailability and 'yes' to at least three drug-like items. Subsequently, the toxicity of the five functional constituents was evaluated using the Pro Tox-3.0 database[24], which predicted a toxicity level of 3 for quercetin, indicating possible toxic effects. Therefore, no subsequent target prediction was performed for this constituent. Finally, the target genes of the other four components were obtained in the SwissTargetPrediction database.

2.8.2 Acquisition of CVD-related genes

Using 'cardiovascular disease' as a search term, we searched for CVD-related genes in the GeneCards and Online Mendelian Inheritance Database for Humans (OMIM) databases, integrated the results of the two databases, and deleted duplicates.

Meanwhile, the GSE6054 dataset was selected from the GEO database to further refine the screening of CVD-related genes. Transcriptome data were normalized using R software, and differential expression analysis was performed using the limma package to identify differentially expressed genes[20]. Weighted correlation network analysis (WGCNA) was also performed to construct gene co-expression networks, aiming to identify the two modules with the highest correlation with the traits, using key genes as a basis[21].

The genes obtained by the three methods were integrated, and duplicates were removed to obtain the CVD-related target genes.

2.8.3 Immune cell infiltration analysis

Immune cell infiltration analysis of the differentially expressed genes was performed using the R software and the CIBERSORT program package to explore the differences in immune cells between the disease and normal groups.

2.8.4 Constructing protein interaction networks

After obtaining the intersections of the four functional components of Phyllanthus emblica with the CVD-related target genes, the intersected genes were entered into the STRING database to construct a protein-protein interaction (PPI) network. The species was restricted to “Homo sapiens”, and the interaction confidence threshold was set to 0.40. The PPI network was then visualized using Cytoscape 3.8.1 software to identify key nodes, and the top 50 genes, ranked by node degree, were selected as potential targets.

2.8.5 Screening of cardiovascular key effector genes

Three predictive models — Support Vector Machine (SVM), Random Forest (RF), and Lasso regression — were constructed to identify the key effect targets by screening the top 50 potential targets. The results obtained from the three machine learning algorithms were intersected to obtain the final key effect targets.

2.8.6 Validation of key effector genes

The accuracy of the key effect genes was verified by logistic regression modelling and receiver operating characteristic curves (ROC). An area under the ROC curve (AUC) of less than 0.7 is considered low, 0.7-0.9 is moderate, and greater than 0.9 is high[22].

2.8.7 Molecular docking

The four Phyllanthus emblica functional components were molecularly docked with the obtained key effector genes to explore their interactions. The two-dimensional structures of the four functional components were obtained from the PubChem database, and the corresponding gene proteins were identified in the UniProt database and subsequently downloaded into the PDB database. The structures were optimized using ChemDraw software. The active sites of protein receptors were analyzed using AutoDock Tools 1.5.7, and molecular docking was performed using AutoDock Vina. Finally, the results were visualized using Pymol.

2.8.8 Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis

Gene ontology (GO) enrichment analysis of biological processes (BP), molecular functions (MF), and cellular components (CC), as well as KEGG pathway enrichment analysis of key effector genes, were performed using the R software clusterProfiler and enrichplot packages, and the results were visualized.

2.9 Mendelian randomization probes causal relationships between key effector genes and disease

Causal associations between key effector genes and CVD were explored using two-sample Mendelian randomization. SNPs of key effector genes were obtained from the IEU database as exposure, and CVD SNPs were obtained from the FinnGen database as outcome, respectively. Mendelian randomization was performed using the R software and the TwoSampleMR package, and the association between the expression levels of key effector genes and the risk of CVD was assessed using the inverse variance weighting (IVW) method.

2.10 Statistical analysis

Meta-analysis was performed using Stata 17 and RevMan 5.4 software. Measurement data were expressed as standardized mean differences (SMD) and their 95% confidence intervals, and count data were expressed as the ratio of ratios (OR) and their 95% confidence intervals. Heterogeneity between the results of the included studies was analyzed using the χ^2 test (p-value $\alpha = 0.1$), and the magnitude of heterogeneity was quantified by incorporating the I^2 statistic. According to the definition in the Cochrane Handbook, heterogeneity with an I^2 between 0% and 40% may not be significant, an I^2 between 30% and 60% represents moderate heterogeneity, an I^2 between 50% and 90% represents substantial heterogeneity, and an I^2 between 75% and 100% represents considerable heterogeneity[23]. According to Cochrane's recommendations, this paper employed a random-effects model for the meta-analysis. The test level for meta-analysis was set at $\alpha = 0.05$. Funnel plots were used to detect publication bias in the literature.

3. Results

3.1 Literature search process and results

A total of 725 articles were obtained from the initial screening, and six articles that met the criteria were selected after a layer-by-layer screening process. The search revealed that relevant clinical trials were predominantly conducted in India, a finding consistent with the traditional use of Phyllanthus emblica in Ayurvedic medicine. While this regional focus supports cultural consistency in herbal preparation and use, it may limit the generalizability of findings to other populations. The specific screening process and results are shown in Figure 2. The basic characteristics of the included articles are presented in Table 1, and the evaluation of the literature quality is shown in Table S1 and Figure S1.

Table 1. Characteristics of included studies (all conducted in India).

First author	Location	Year	Sample size	Gender	Age	course of treatment	Intervention material	Outcome indicators
			Total (Intervention/ Control)	male/female	Intervention/ Control			
Upadya[25]	India	2019	98（49/49）	45/53	42.2±9.20/40.7±10.13	Twice a day for 12 weeks	Phyllanthus emblicai Extract Capsules 500mg	①②③④⑤

Usharani[26]	India	2019	39（21/18）	29/10	57.24±8.94/56.89±7.39	Twice a day for 12 weeks	Phyllanthus emblicai Extract Capsules 500mg	①②③④⑥⑦⑧⑨
Usharani[27]	India	2013	40（20/20）	27/13	57.75±9.86/56.90±9.17	Twice a day for 12 weeks	Phyllanthus emblicai Extract Capsules 500mg	①②③④⑤⑥⑦⑧⑨
Shanmugarajan[28]	India	2021	150（75/75）	119/31	58.8±8.68/60.0±9.42	Twice a day for 12 weeks	Phyllanthus emblicai Extract Capsules 500mg	①②③④⑤⑨
Biswas[29]	India	2014	30（20/10）	——	——	Twice a day for 60 days	Phyllanthus emblicai Extract Capsules 250mg	①②③④⑤⑨
Usharani[30]	India	2014	20（10/10）	3/17	60.1±6.471/58.6±10.54	Twice a day for 12 weeks	Phyllanthus emblicai Extract Capsules 500mg	①②③④⑥⑦⑧

Outcome indicators: ①TG②TC③LDL④HDL⑤VLDL⑥NO⑦GSH⑧MDA⑨hsCRP.

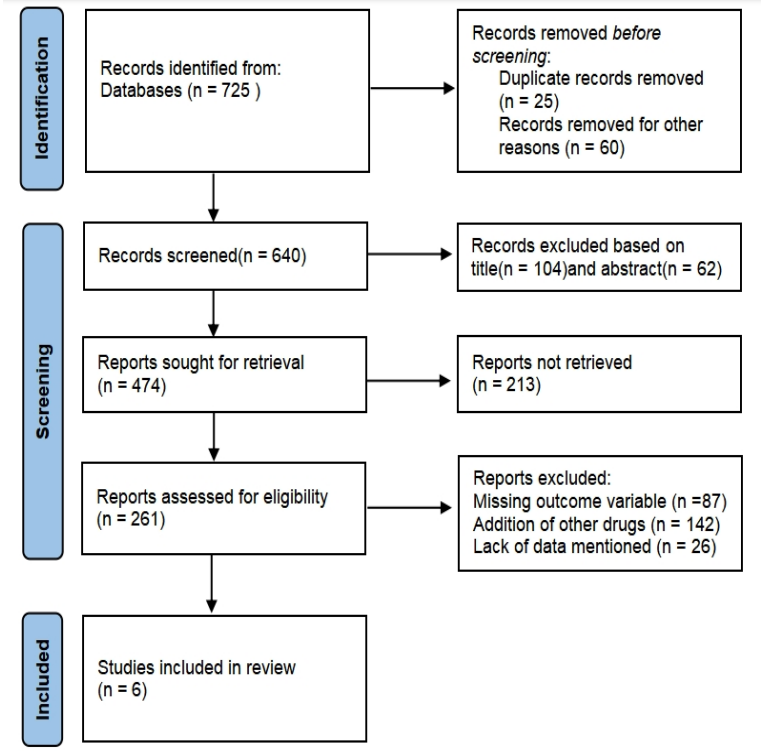


Figure 2. Flowchart of literature screening

3.2 Meta-analysis

3.2.1 Meta-analysis of key outcome indicators

All six articles reported lipid index results. As can be seen from the forest plot, the heterogeneity of the included literature was high ($P < 0.05$, I^2=88.2%), but meta-regression analyses did not identify specific sources of heterogeneity. The combined sample size of all the literature was 397 cases. The results for all five indicators were statistically significant [TG: OR=0.69, 95%CI=(-0.00,1.38), $P < 0.05$; TC: OR=0.69, 95%CI=(0.23,1.14), $P < 0.05$; LDL: OR=0.93, 95%CI=(0.23,1.63), $P < 0.05$; HDL: OR=-0.80, 95%CI=(-1.59,-0.02), $P < 0.05$; VLDL: OR=0.39, 95%CI=(-0.01,0.78), $P < 0.05$] (Figure 3). The results showed that compared with the control group, the use of Phyllanthus emblica extract capsule for intervention significantly reduced triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), and very

low-density lipoprotein (VLDL) concentrations and elevated high-density lipoprotein (HDL) concentrations in patients with CVD, suggesting that Phyllanthus emblica has a certain degree of improvement of lipid indices of patients with CVD.

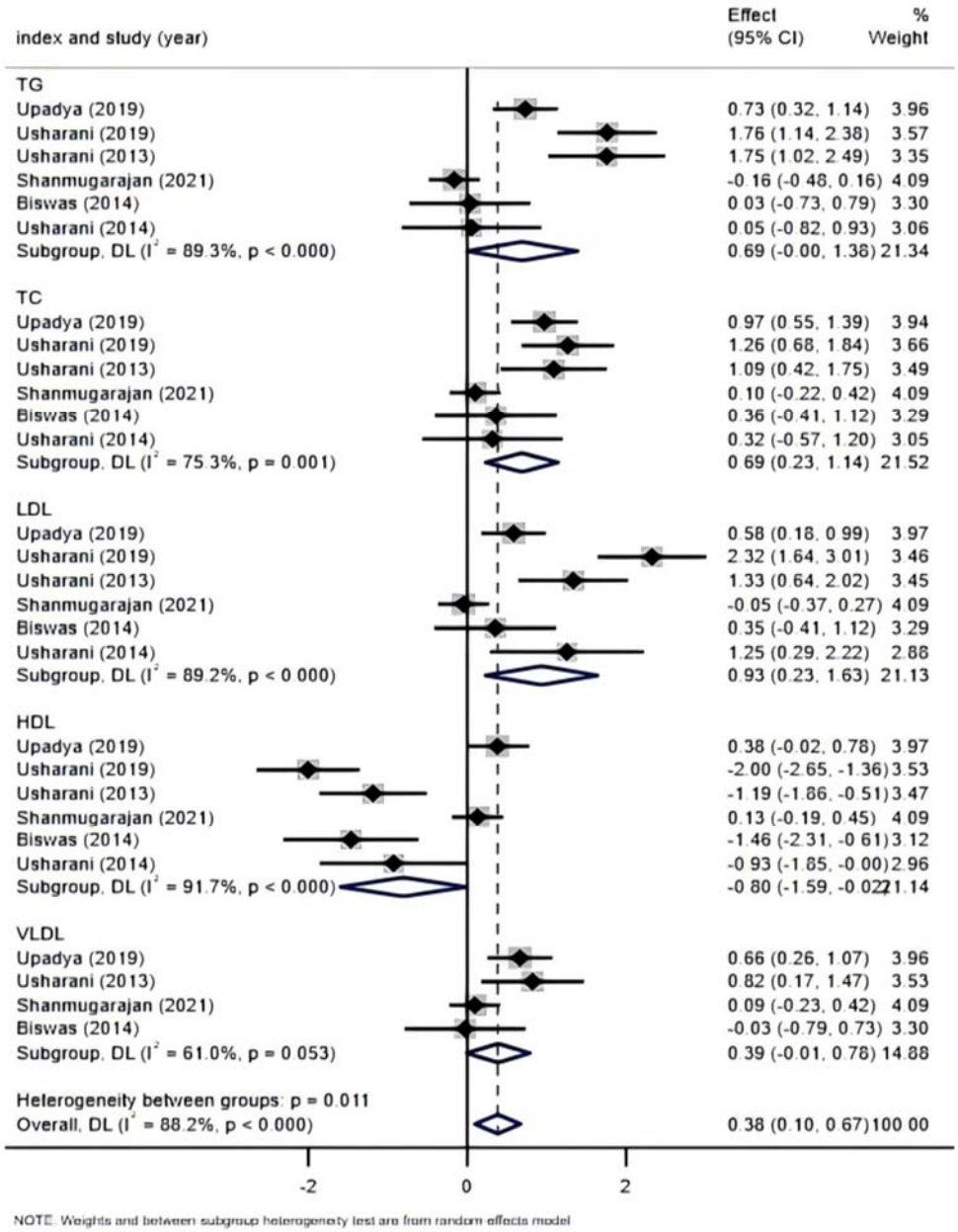


Figure 3. Forest plot for meta-analysis of key indicators

3.2.2 Meta-analysis of secondary outcome indicators

Three of the six articles reported on nitric oxide (NO), glutathione (GSH), and malondialdehyde (MDA) levels, and four reported on high-sensitivity C-reactive protein (hsCRP) levels. As can be seen from the forest plot, the results of all four indicators were statistically significant[NO: OR=-2.31, 95%CI=(-3.86,-0.95), $P < 0.05$; GSH: OR=-2.20, 95%CI=(-4.15,-0.26), $P < 0.05$; MDA: OR=1.25, 95%CI=(-0.03, 2.53), $P < 0.05$; hsCRP: OR=1.36, 95%CI=(0.12,2.60), $P < 0.05$] (Figure 4). The results showed that intervention with Phyllanthus emblica extract capsules significantly reduced MDA and hsCRP levels, while elevating NO and GSH levels, in patients with CVD compared to the control group.

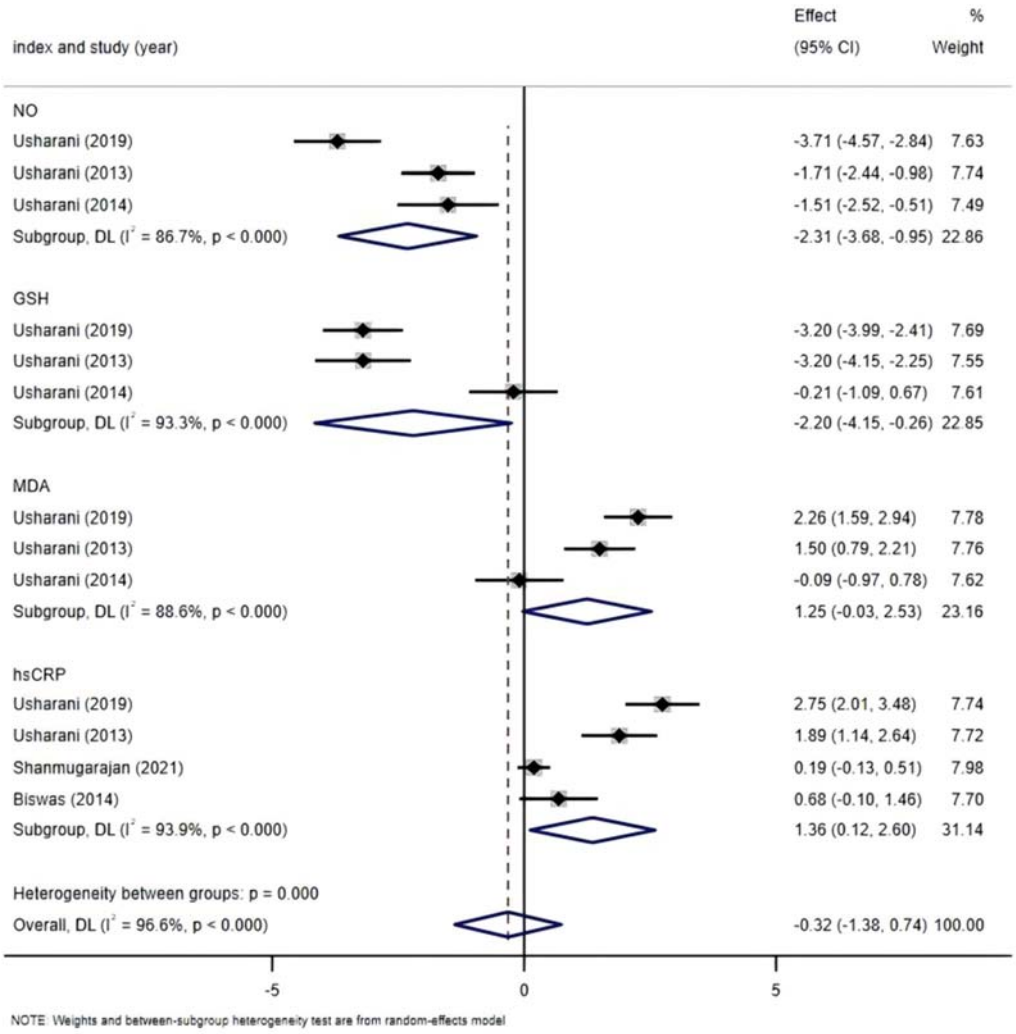


Figure 4. Forest plot for meta-analysis of secondary indicators

The results of this meta-analysis suggest a potential beneficial trend of Phyllanthus emblica and its functional components on cardiovascular health. The underlying mechanisms are not fully elucidated, but they may involve the regulation of lipid metabolism and the enhancement of antioxidant capacity. It is crucial to note that these findings, while promising, are preliminary and derived from studies with limitations (such as geographical concentration in India and high heterogeneity). Therefore, they should be interpreted as a justification for further investigation rather than as evidence supporting immediate clinical application. Despite these limitations, the consistent trend provides a strong rationale for future research. Based on this rationale, we have initiated subsequent investigations to identify the specific bioactive components responsible for these potential effects.

3.2.3 Meta-regression analysis

Due to the high heterogeneity of the included studies, meta-regression analysis was performed on five primary outcome measures to explore the sources of heterogeneity. Based on the data from the included studies, analyses were conducted on the duration and dose of the intervention. The results for all five outcome measures were not statistically significant, suggesting that intervention duration and intervention dose may not be the primary sources of heterogeneity. The main results are shown in Table 2.

Table 2. Meta-regression analysis results

	_ES	Coefficient	Std. err.	t	*P*	95%CI	
TG	Intervention duration	-0.7803566	1.020473	-0.76	0.487	-3.613644	2.052931
	Intervention dose	-0.7803566	1.020473	-0.76	0.487	-3.613644	2.052931
	_cons	1.593982	1.239291	1.29	0.268	-1.846841	5.034805
TC	Intervention duration	-0.3813212	0.6482455	-0.59	0.588	2.181139	1.418497
	Intervention dose	-0.3813212	0.6482455	-0.59	0.588	2.181139	1.418497
	_cons	1.120939	0.7722416	1.45	0.22	1.023148	3.265025
LDL	Intervention duration	-0.6955753	1.030969	-0.67	0.537	3.558004	2.166853
	Intervention dose	-0.6955753	1.030969	-0.67	0.537	3.558004	2.166853
	_cons	1.743282	1.253266	1.39	0.237	1.736342	5.222906
HDL	Intervention duration	-0.7770317	1.140753	-0.68	0.533	-3.94427	2.390206
	Intervention dose	-0.7770317	1.140753	-0.68	0.533	-3.94427	2.390206
	_cons	0.0906192	1.381127	0.07	0.951	-3.744004	3.925242
VLDL	Intervention duration	-0.5030259	0.5558823	-0.9	0.461	-2.894794	1.888743
	Intervention dose	-0.5030259	0.5558823	-0.9	0.461	-2.894794	1.888743
	_cons	0.9781398	0.6839708	1.43	0.289	-1.964749	3.921029

3.2.4 Subgroup Analysis

Further subgroup analysis was conducted based on intervention duration and dose. Intervention duration was categorized into “Twice a day for 12 weeks” and “Twice a day for 60 days,” while intervention dose was categorized into “Phyllanthus emblica extract capsules 500 mg” and “Phyllanthus emblica extract capsules 250 mg.” The results showed that heterogeneity persisted at a high level. This suggests that the high heterogeneity may be due to differences in baseline characteristics of patients, variations in drug formulation, administration methods, or adherence, as well as differences in lipid profile measurements due to varying testing methods, sampling times, or laboratory standards. The results of the subgroup analysis are presented in Tables 3 and 4, as well as Figures S2 and S3.

Table 3. Results of subgroup analysis by intervention duration

Primary outcome measures	Subgroup	Number of studies	Adverse reaction subgroup analysis results		
			OR(95%CI)	Heterogeneity I^2	*P*
TG	12 weeks	5	27.79(6.93,48.67)	78%	0.009
	60 days	1	2.00(-45.76,49.76)	0%	0.930
TC	12 weeks	5	22.04(8.21,35.87)	75%	0.002
	60 days	1	12.70(-14.62,40.02)	0%	0.360
LDL	12 weeks	5	22.27(6.80,37.75)	88%	0.001
	60 days	1	10.40(-10.65,31.45)	0%	0.330
HDL	12 weeks	5	-3.12(-7.78,1.53)	91%	0.001
	60 days	1	-8.50(-12.53,-4.47)	0%	0.001
VLDL	12 weeks	5	6.19(2.34,10.03)	29%	0.002
	60 days	1	-0.40(-11.62,10.82)	0%	0.940

Table 4. Results of subgroup analysis by intervention dose

Primary outcome measures	Subgroup	Number of studies	Adverse reaction subgroup analysis results		
			OR(95%CI)	Heterogeneity I^2	*P*
TG	500mg	5	27.79(6.93,48.67)	78%	0.009
	250mg	1	2.00(-45.76,49.76)	0%	0.930
TC	500mg	5	22.04(8.21,35.87)	75%	0.002
	250mg	1	12.70(-14.62,40.02)	0%	0.360
LDL	500mg	5	22.27(6.80,37.75)	88%	0.001
	250mg	1	10.40(-10.65,31.45)	0%	0.330
HDL	500mg	5	-3.12(-7.78,1.53)	91%	0.001

	250mg	1	-8.50(-12.53,-4.47)	0%	0.001
VLDL	500mg	5	6.19(2.34,10.03)	29%	0.002
	250mg	1	-0.40(-11.62,10.82)	0%	0.940

3.2.5 Sensitivity analysis

The sensitivity analysis results of the five primary outcome measures showed differences in the effect size estimates and their 95% CIs among the studies, indicating a certain degree of heterogeneity (Figure S4).

3.2.6 Publication bias

A publication bias analysis was conducted for five primary outcome measures, with quantitative assessments using the Egger and Begg tests. The Egger test results showed that the P-value for the HDL indicator was <0.05, suggesting publication bias may exist for this indicator. The Egger and Begg test results for the other outcome measures were all $P > 0.05$, suggesting no publication bias (Tables 5 and 6).

Table 5. Egger test results for publication bias

Primary outcome measures	Std_Eff	Coefficient	Std. err.	t	*P*	95%CI	
TG	**slope**	-0.4563967	0.8709371	-0.52	0.628	-2.874506	1.961712
	bias	3.79005	3.354177	1.13	0.322	-5.522638	13.10274
TC	**slope**	0.065379	0.6211691	0.11	0.921	-1.659263	1.790021
	bias	2.132707	2.417064	0.88	0.427	-4.57814	8.843553
LDL	**slope**	-0.7131394	0.6727639	1.06	0.349	-2.581031	1.154753
	bias	5.270571	2.576472	2.05	0.11	-1.882862	12.424
HDL	**slope**	1.34422	0.6293492	2.14	0.1	-0.4031337	3.091573
	bias	-6.819996	2.421967	-2.82	0.048	-13.54445	-0.0955376
VLDL	**slope**	0.0849104	0.6639197	0.13	0.91	-2.771705	2.941526
	bias	1.195516	2.903647	0.41	0.72	-11.29787	13.6889

Table 6. Begg test results for publication bias

Primary outcome measures	Kendall's score	SE of score	z	*P*
TG	1	5.323	0	1
TC	-3	5.323	-0.75	0.7071
LDL	3	5.323	0.38	0.7071
HDL	-3	5.323	-0.75	0.7071
VLDL	0	2.944	-0.34	1

The symmetry of the funnel plot is used to determine publication bias in the selected literature. When all literature is evenly distributed in the funnel plot, it indicates minimal publication bias and high confidence in the results. Conversely, when literature is unevenly distributed in the funnel plot, it indicates significant publication bias. The funnel plots of the five primary outcome measures show that the distribution of all literature in the funnel plot is symmetrical, suggesting no publication bias (Figure S5).

3.3 Screening of functional components of Phyllanthus emblica and identification of target genes

A total of 18 functional constituents of Phyllanthus emblica were screened in the TCMSP database with OB ≥ 30% and DL ≥ 0.18. Five functional constituents, namely ellagic acid, luteolin, Phyllanthin, kaempferol, and quercetin, were further screened in combination with the SwissADME database under the filtering conditions of “high” oral bioavailability and “yes” for at least three similar drugs. The toxicity of the five functional constituents was evaluated using the Pro Tox 3.0 database[24]. The toxicity grades were luteolin grade 5 and kaempferol grade 5, suggesting possible slight harm. Ellagic acid grade 4 and Phyllanthin grade 4,

suggesting a potentially harmful effect. Quercetin is grade 3, suggesting a potentially toxic effect. The toxicity and properties of the components are shown in Figure 5 and Table 7.

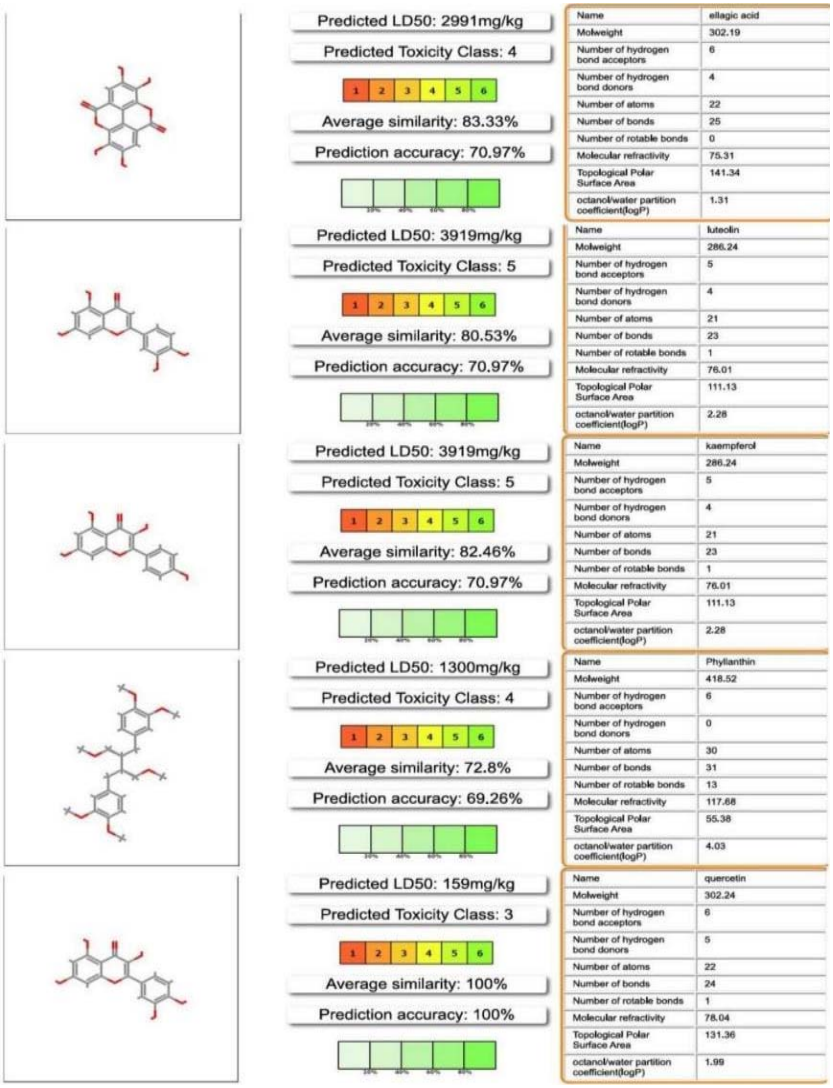


Figure 5. Toxicity prediction chart

Table 7. Properties of functional components

Mol ID	Molecule Name	MW	AlogP	Hdon	Hacc	OB（%）	Caco-2	BBB	DL	FASA-	HL
MOL001002	ellagic acid	302.20	1.48	4	8	43.06	-0.44	-1.41	0.43	0.43	-1.04
MOL000422	kaempferol	286.25	1.77	4	6	41.88	0.26	-0.55	0.24	0.00	14.74
MOL000006	luteolin	286.25	2.07	4	6	36.16	0.19	-0.84	0.25	0.39	15.94
MOL006812	Phyllanthin	418.58	4.11	0	6	33.31	1.06	0.57	0.42	0.15	3.36
MOL000098	quercetin	302.25	1.50	5	7	46.43	0.05	-0.77	0.28	0.38	14.40

In this section, active components with favorable pharmacokinetic properties were screened from Phyllanthus emblica. Their potential toxicity risks were quantified, and their safety was evaluated. The results indicate that although the five functional components identified exhibit high oral bioavailability, their toxicity profiles show significant differences. Among them, quercetin was excluded from subsequent analysis due to its potential toxicity. Conducting dual efficacy and safety evaluations is crucial during the development of new drugs. This approach not only provides a reliable compound foundation for subsequent mechanism studies and disease-related target prediction of Phyllanthus emblica's functional components but also offers a scientific basis for selecting safe and effective functional components and implementing risk control in future

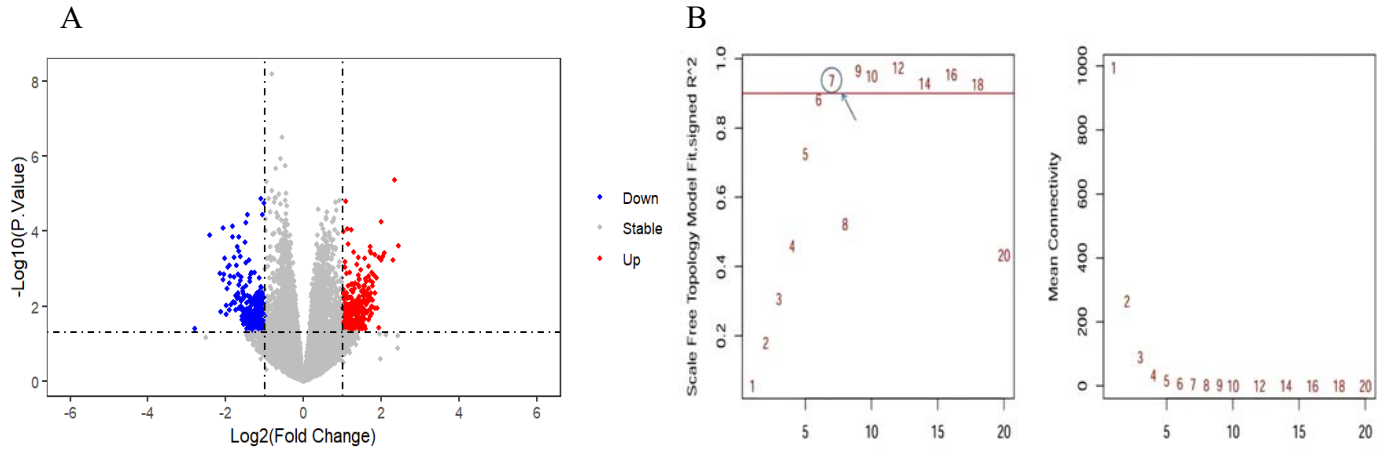
clinical applications. It holds significant methodological reference value for component optimization and early toxicity warning in the modern development of food-medicine dual-use substances.

3.4 Identification of cardiovascular disease-related target genes

The GeneCards and OMIM databases were searched for related genes using the search term "cardiovascular disease". The initial search in the GeneCards database yielded 16,270 results, and 5121 genes were further screened based on the average Relevance score. The OMIM database yielded 383 genes. A total of 5125 genes were obtained by combining the results from the two databases and removing duplicates.

Based on the meta-analysis results, the GSE6054 dataset was selected from the GEO database to further refine the screening of CVD-related genes. By performing differential gene analysis on the normal and disease groups, 669 differentially expressed genes were identified (Figure 6A). Subsequently, WGCNA analysis was performed on the dataset to construct gene co-expression networks. A scale-free network was constructed with a correlation coefficient of 0.9 and a soft threshold of 7 (Figure 6B). The genes were clustered into sections based on a cut height of 0.25 (Figure 6C). Two modules with strong and statistically significant correlation (cor=0.41, $P < 0.05$) were selected for further analysis (Figure 6D, 6E), and a total of 3570 key genes were obtained from the two modules.

This section identifies the most reliable potential target genes for CVD from thousands of candidates by integrating multiple database resources and employing bioinformatics methods, including differential expression analysis and WGCNA. After integrating genes obtained from three methods and removing duplicates, a final set of 8,094 disease-related target genes was obtained. The reliability of results derived from multiple analytical approaches far exceeds that of single-method analyses. This not only significantly expands our understanding of the genetic basis of CVD but also provides a high-quality, highly credible candidate gene target library for subsequent in-depth studies of their molecular mechanisms. The comprehensive and multi-tiered nature of the screening process holds significant scientific value and practical implications for precision medicine research and translational applications in CVD.



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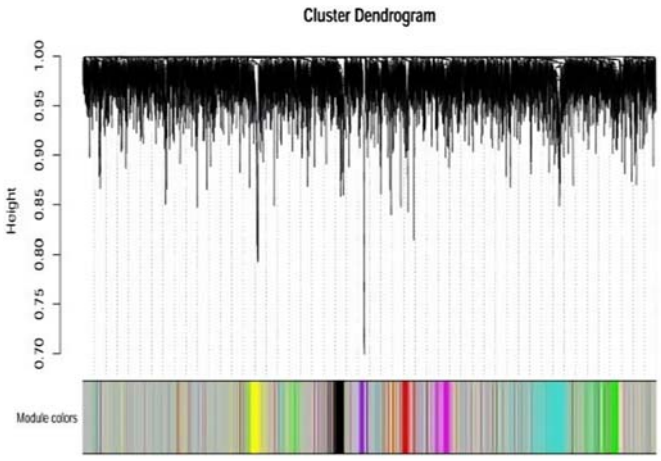

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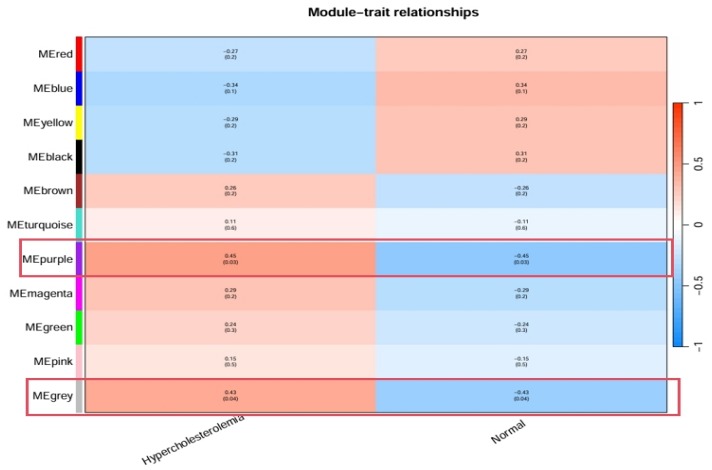

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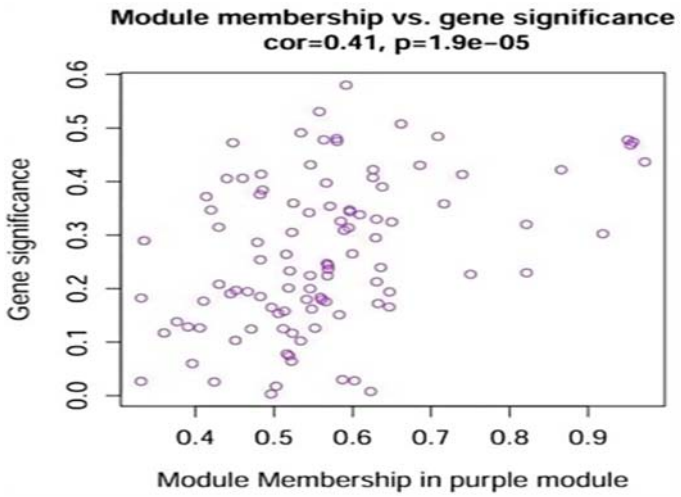

Figure 6. (A) Analysis of variance volcano plot (B) Soft-threshold scale-free network (C) Modules of genes associated with traits (D) Modules of highly correlated genes (E) Modules of genes trait relationship plot

3.5 Immune cell infiltration analysis

The differentially expressed genes were analyzed for immune cell infiltration to compare the differences in immune cells between the normal and disease groups. The type and amount of immune cells expressed in each sample were determined, and the results are shown in Figure 7A. The differences in immune cell types between the two groups were also analyzed. As shown in Figure 7B, the immune cell types significantly upregulated in the Hypercholesterolemia group include: memory B cells, plasma cells, CD8 T cells, γδ T cells, activated NK cells, monocytes, M0 macrophages, M1 macrophages, activated mast cells, eosinophils, and neutrophils. The significantly downregulated immune cell types included resting memory CD4 T cells, NK cells, M2 macrophages, and mast cells.

Based on the analysis of immune cell infiltration, this study identified widespread dysregulation of the immune microenvironment in CVD states associated with hypercholesterolemia. This dysregulation is characterized by a marked increase in the infiltration of pro-inflammatory immune cells (such as M1

macrophages, activated NK cells, and various effector T cells). In contrast, immune cells with anti-inflammatory or regulatory functions (such as M2 macrophages and resting memory CD4 T cells) are significantly reduced. This suggests that immune-inflammatory responses play a crucial role in the onset and progression of CVD, with the disease microenvironment exhibiting a distinct pro-inflammatory polarization state.

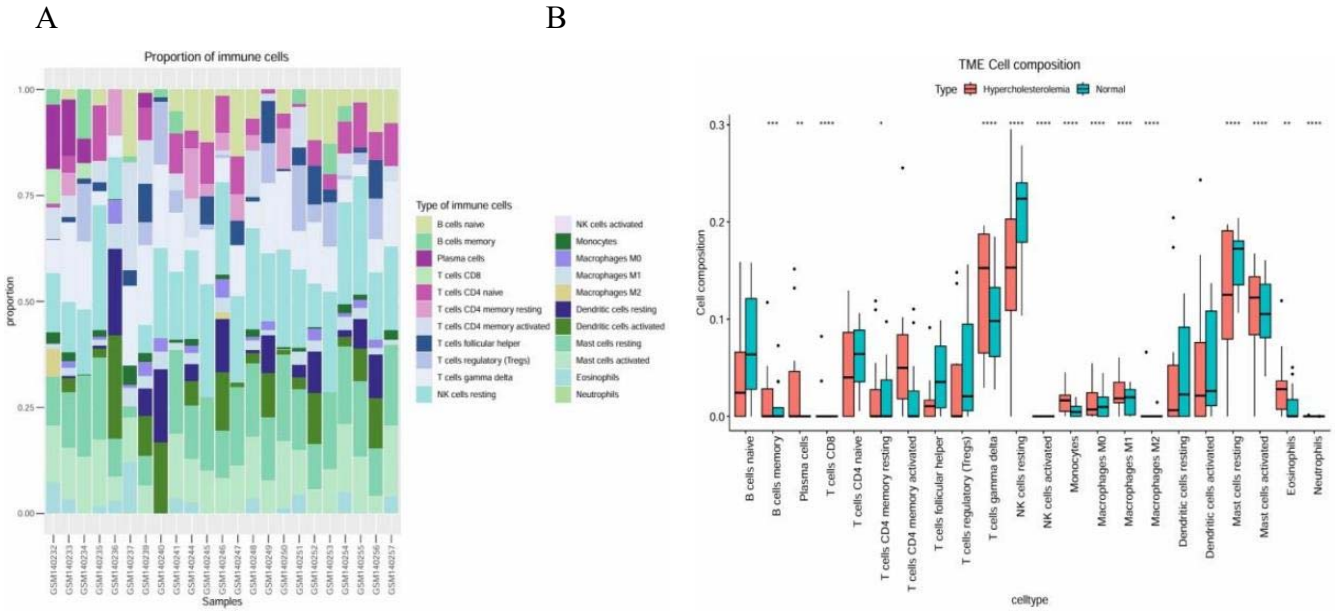

Figure 7. (A) Plot of immune cell type and content (B) Box plot of immune cell fraction in normal and disease groups

3.6 PPI Network Analysis

A total of 160 intersecting genes, including those of Phyllanthus emblica and CVD target genes, were obtained by importing them into the Jveen website. Subsequently, the STRING database was imported to construct the PPI interaction network. Gene importance was ranked using Cytoscape 3.8.1 software. The top 50 genes were selected for subsequent analysis (Figure 8, Table 8).

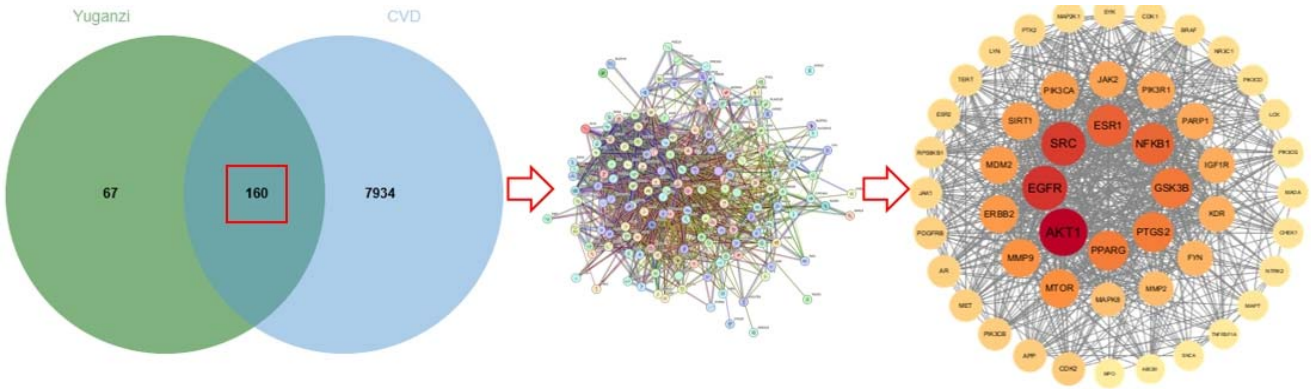

Figure 8. PPI network diagram

Table 8. Properties of functional components

Gene Symbol	Protein Name	Degree
AKT1	AKT Serine/Threonine Kinase 1	93
EGFR	Epidermal Growth Factor Receptor	81
SRC	SRC Proto-Oncogene, Non-Receptor Tyrosine Kinase	77
ESR1	Estrogen Receptor 1	70
NFKB1	Nuclear Factor Kappa B Subunit 1	69

GSK3B	Glycogen Synthase Kinase 3 Beta	64
PTGS2	Prostaglandin-Endoperoxide Synthase 2	63
PPARG	Peroxisome Proliferator Activated Receptor Gamma	62
MTOR	Mechanistic Target Of Rapamycin Kinase	59
MMP9	Matrix Metallopeptidase 9	58
ERBB2	Erb-B2 Receptor Tyrosine Kinase 2	56
MDM2	MDM2 Proto-Oncogene	55
SIRT1	Sirtuin 1	54
PIK3CA	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha	54
JAK2	Janus Kinase 2	52
PIK3R1	Phosphoinositide-3-Kinase Regulatory Subunit 1	51
PARP1	Poly(ADP-Ribose) Polymerase 1	49
IGF1R	Insulin Like Growth Factor 1 Receptor	49
KDR	Kinase Insert Domain Receptor	48
FYN	FYN Proto-Oncogene, Src Family Tyrosine Kinase	46
MMP2	Matrix Metallopeptidase 2	44
MAPK8	Mitogen-Activated Protein Kinase 8	42
CDK2	Cyclin Dependent Kinase 2	39
APP	Amyloid Beta Precursor Protein	38
PIK3CB	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Beta	38
MET	MET Proto-Oncogene, Receptor Tyrosine Kinase	37
PDGFRB	Platelet Derived Growth Factor Receptor Beta	37
AR	Androgen Receptor	37
ESR2	Estrogen Receptor 2	34
RPS6KB1	Ribosomal Protein S6 Kinase B1	34
TERT	Telomerase Reverse Transcriptase	34
PTK2	Protein Tyrosine Kinase 2	34
LYN	LYN Proto-Oncogene, Src Family Tyrosine Kinase	34
JAK1	Janus Kinase 1	33
SYK	Spleen Associated Tyrosine Kinase	33
MAP2K1	Mitogen-Activated Protein Kinase Kinase 1	33
CDK1	Cyclin Dependent Kinase 1	33
NR3C1	Nuclear Receptor Subfamily 3 Group C Member 1	32
BRAF	B-Raf Proto-Oncogene, Serine/Threonine Kinase	32
PIK3CD	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Delta	31
LCK	LCK Proto-Oncogene, Src Family Tyrosine Kinase	31
NTRK2	Neurotrophic Receptor Tyrosine Kinase 2	30
MAOA	Monoamine Oxidase A	30
CHEK1	Checkpoint Kinase 1	30
PIK3CG	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Gamma	29
MAPT	Microtubule Associated Protein Tau	29
SNCA	Synuclein Alpha	28
TNFRSF1A	TNF Receptor Superfamily Member 1A	27
ABCB1	ATP Binding Cassette Subfamily B Member 1	27
MPO	Myeloperoxidase	27

3.7 Screening for key effector genes

Three machine learning algorithms were utilized to further screen key effector genes among the top 50 target genes. The SVM algorithm showed the lowest error when the number of features was 23 (Figure 9A). The Random Forest algorithm showed the highest accuracy when the number of genes was 42. The top 20 genes in terms of importance were also screened (Figure 9B-D), and 19 genes were obtained after merging and deleting duplicates. Lasso regression analysis identified seven genes as yielding the best model fit (Figure 9E). The crossover of the genes obtained from the three machine learning algorithms ultimately yielded seven key effect genes: AKT1, ABCB1, FYN, IGF1R, NR3C1, PIK3CA, and SYK (Figure 9F). Through screening, seven “core” genes with key effects were ultimately identified from 8094 disease genes, yielding a highly

credible set of candidate targets. These key effector genes are extensively involved in multiple critical biological processes, including inflammatory regulation, cell proliferation and apoptosis, metabolic homeostasis, and signal transduction within the body. This finding also aligns with the results of the meta-analysis at the gene level. The screening of key effector genes not only significantly enhances the accuracy and reliability of the research findings but also provides crucial theoretical foundations and experimental directions for subsequent in-depth exploration of the mechanisms linking these genes to the functional bioactive components of Phyllanthus emblica.

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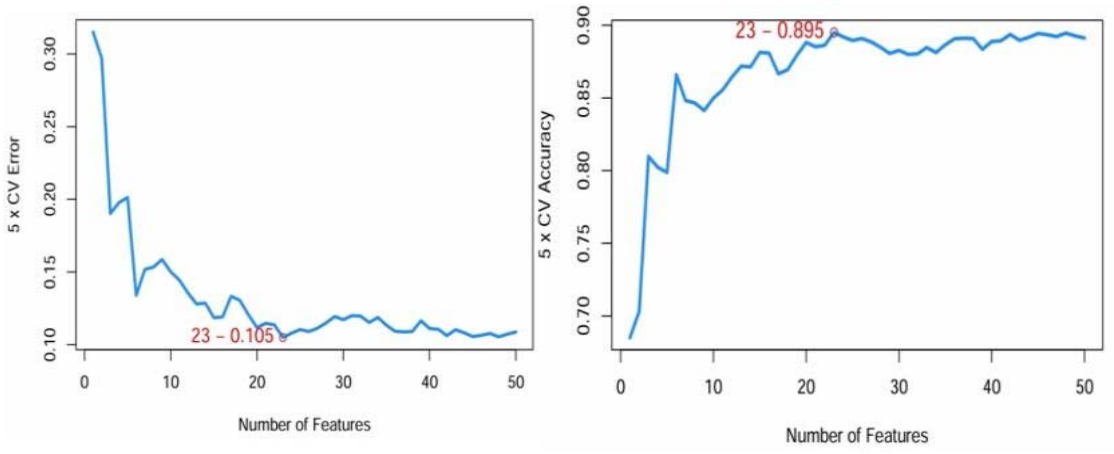

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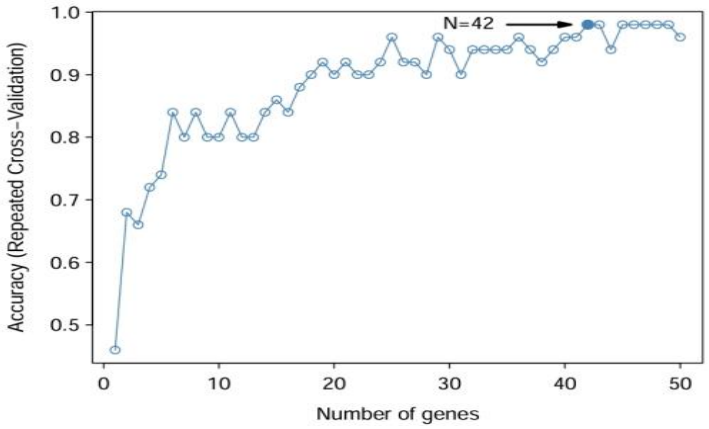

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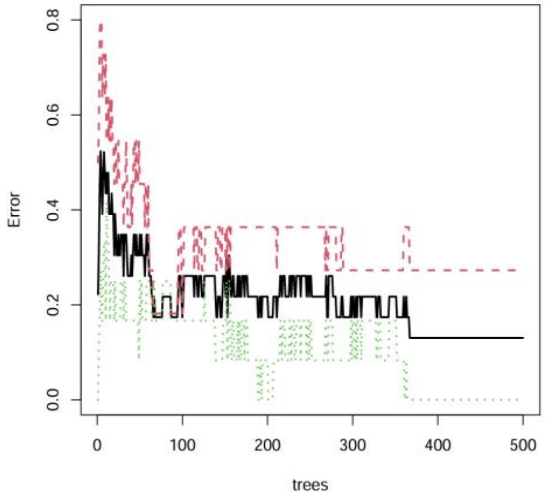

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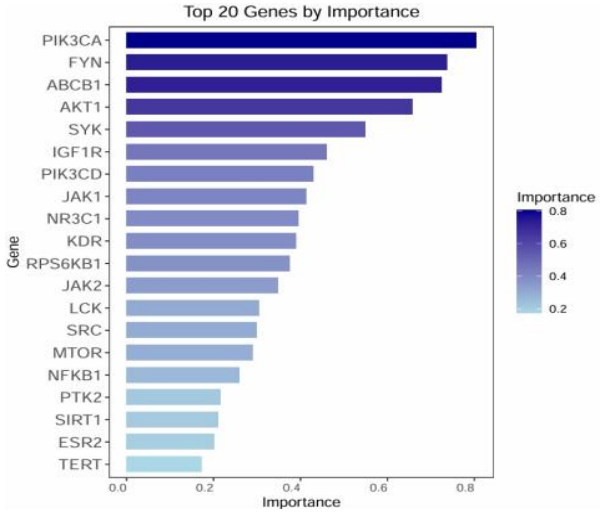

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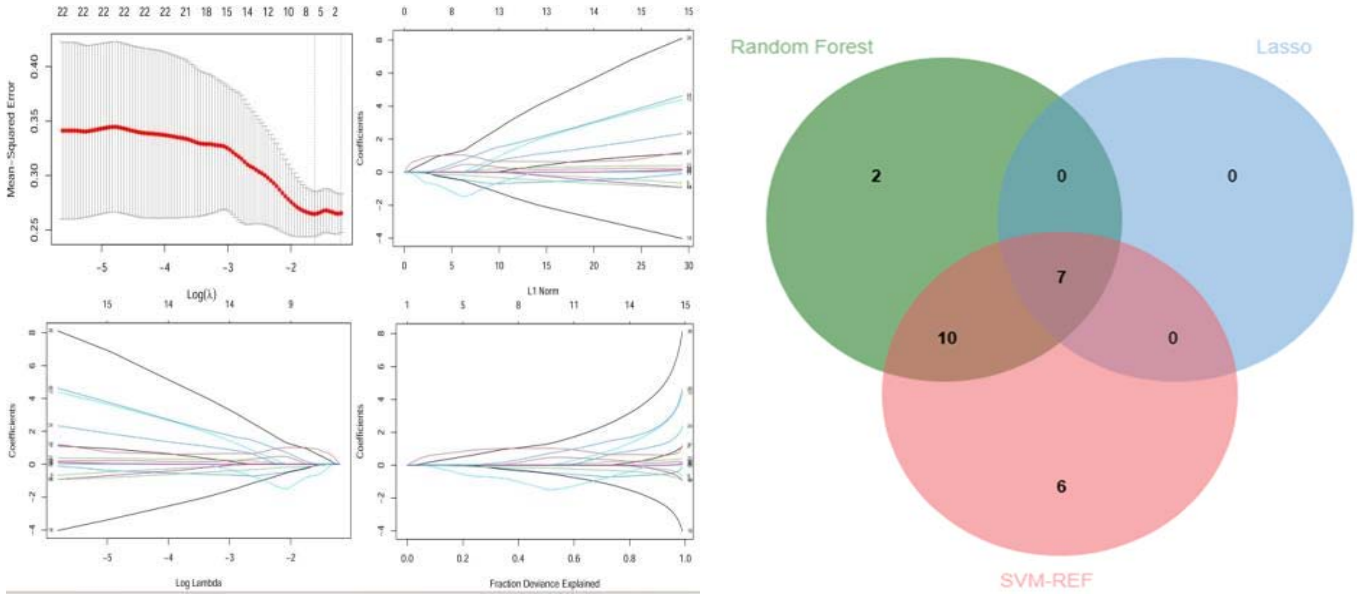

Figure 9. (A) SVM algorithm error rate and accuracy plot (B) Random forest algorithm accuracy plot (C) Random forest algorithm decision tree (D) Random forest algorithm top 20 important genes (E) Lasso regression algorithm (F) Wayne diagram of intersection genes of three machine learning algorithms

3.8 Validating the predicted probability of key effect genes

A predictive column line plot was created to predict the association between key effector genes and CVD, with a statistically significant difference in the total score of 279 for the seven genes (Figure 10A). Further analysis using ROC curves showed that the prediction accuracy of the seven genes was AKT1 (AUC=0.831), ABCB1 (AUC=0.792), FYN (AUC=0.838), PIK3CA (AUC=0.877), SYK (AUC=0.854), NR3C1 (AUC=0.862), and IGF1R (AUC=0.815), all with high prediction accuracy (Figure 10B). Box plots showing the expression levels of the seven key effector genes between the normal and disease groups showed that AKT1 (P=0.0080), FYN (P=0.0086), and SYK (P=0.0026) were significantly up-regulated in the disease group. At the same time, ABCB1 (P=0.0120), IGF1R (P=0.0110), NR3C1 (P=0.0032), and PIK3CA (P=0.0047) were significantly down-regulated in the disease group (see Figure 10C for AKT1 box plots and Figure S6A-F in the Supplementary Material for the remaining six gene box plots).

According to the risk prediction model, the line chart indicates that these genes possess high diagnostic value and predictive accuracy. ROC analysis and differential expression validation jointly confirm the strong association and reliability of these key effect genes with CVD, as evidenced by both predictive accuracy and baseline expression difference. Simultaneously, they further reveal the expression patterns exhibited by these key effect genes under disease conditions. The combination of machine learning predictions and population trial results provides crucial theoretical foundations and data support for developing precision diagnostic tools and novel therapeutic strategies targeting these genes. These genes hold promise as important biomarkers for CVD risk stratification, early intervention, and personalized treatment, as well as potential therapeutic targets.

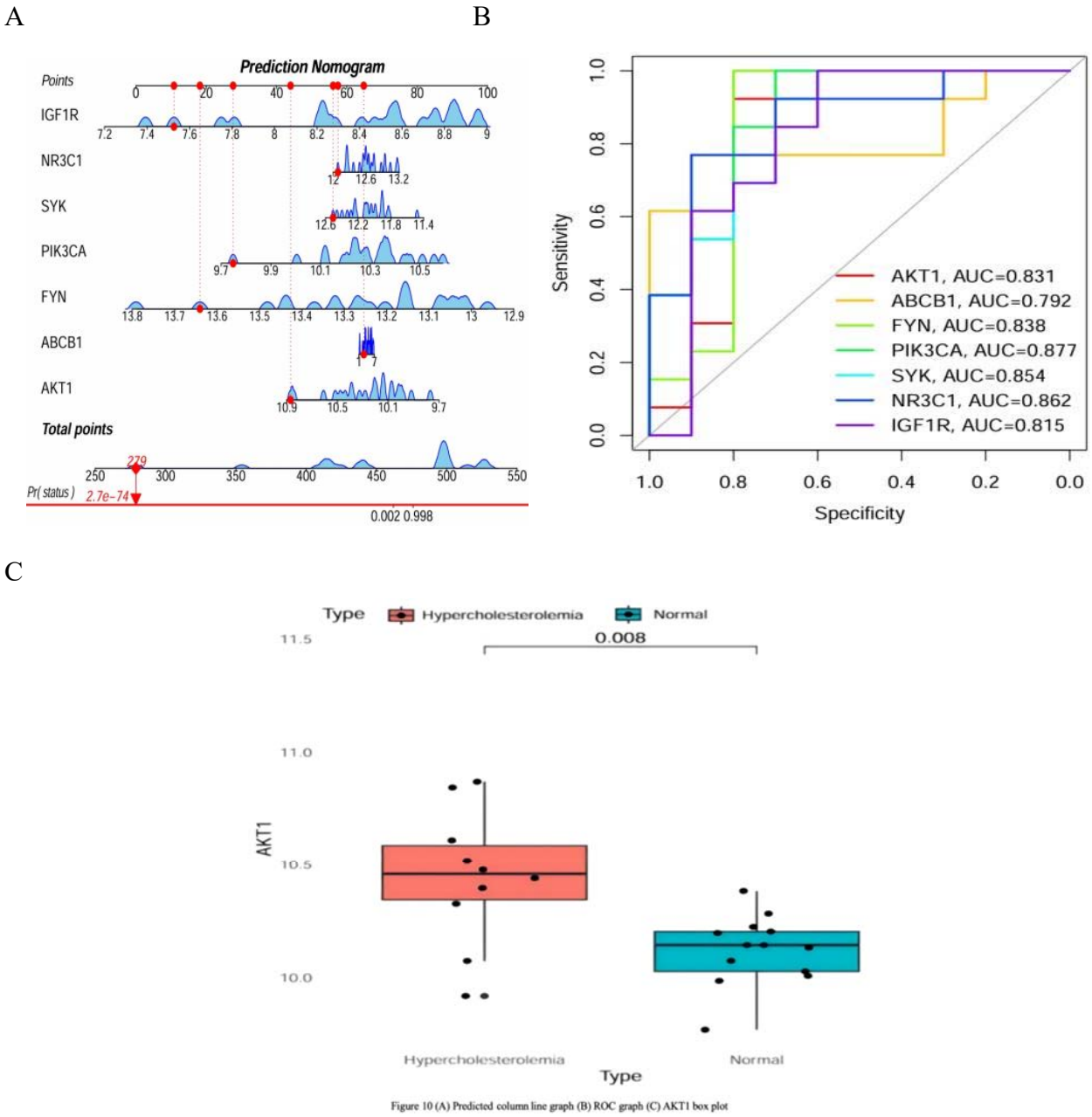

Figure 10. (A) Predicted column line graph (B) ROC graph (C) AKT1 box plot

3.9 Molecular docking

A molecular docking analysis was performed to further explore the relationship between the functional components of Phyllanthus emblica and the key effector genes. The results showed that the binding energies of all docking combinations were less than -4.0 kcal/mol, indicating strong binding of ABCB1 with kaempferol and luteolin, IGF1R with ellagic acid, and SYK with kaempferol and luteolin (Table 9). Molecular docking simulations confirmed, at both the energy and structural levels, the stable and specific binding potential between the primary functional components of Phyllanthus emblica and the proteins encoded by key effector genes in CVD. The binding between each functional component and the effector gene protein receptor primarily occurs through hydrogen bonds. The docking results revealed that Phyllanthus emblica may exert its cardiovascular protective effects by regulating the functions of key signaling proteins through multiple components and multiple targets. The molecular docking model facilitates the rapid and low-cost screening of

compounds from Phyllanthus emblica that bind to specific target proteins. This approach facilitates the analysis and design of molecular interactions, thereby providing a crucial theoretical foundation for subsequent drug design, lead optimization, and mechanistic studies. This advances the modernization of traditional Chinese medicine research. Figure 11 shows the molecular docking diagrams of the two components with the strongest binding energies to the target proteins. The remaining diagrams are provided in Supplementary Material, Figures S7A-L.

Table 9. Molecular binding energies of gene-drugs

Component / Gene	ellagic acid	kaempferol	luteolin	Phyllanthin
AKT1	-6.5	-6.1	-6.3	-4.4
ABCB1	——	-7.0	-7.2	——
FYN	-6.8	——	——	——
IGF1R	-8.3	-7.4	-7.6	-5.0
NR3C1	——	——	——	-6.1
PIK3CA	——	——	——	-4.0
SYK	——	-7.7	-8.1	-6.3

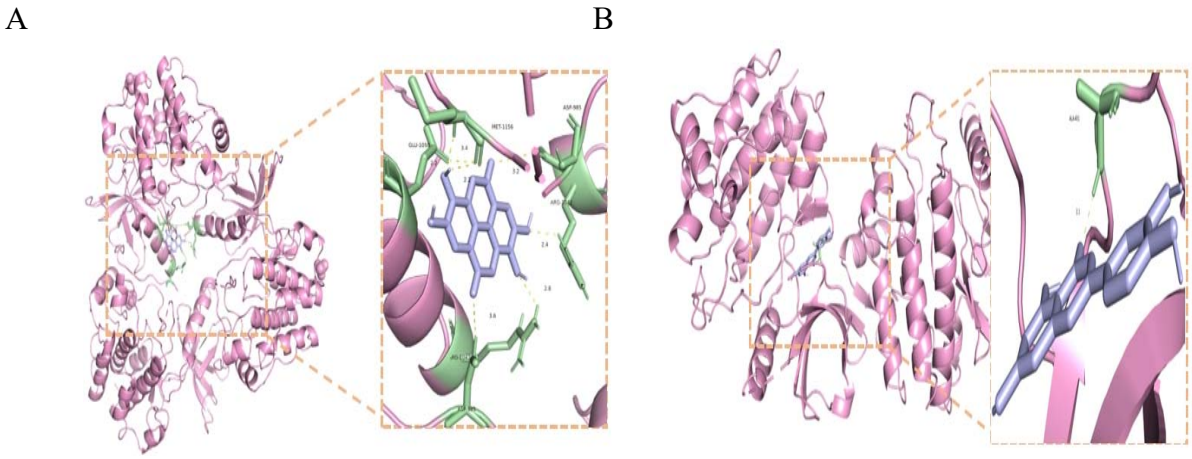

Figure 11. (A) Docking diagram of IGF1R-Ellagic Acid molecule (B) Docking diagram of SYK-luteolin molecule

3.10 GO and KEGG enrichment analysis

Biological function and pathway enrichment analyses of key effector genes were conducted to investigate the mechanism of action of Phyllanthus emblica in relation to CVD on various aspects. According to the GO analysis, the biological process (BP) was primarily related to energy metabolism and immune response, encompassing responses to ketone bodies, dexamethasone, β-amyloid, T-cell co-stimulation, and lymphocyte co-stimulation. Cellular components (CC) are mainly involved in signal transduction and material transport. The molecular function (MF) aspect primarily plays a role in cell signaling, insulin signaling pathways, membrane phospholipid metabolism, and the formation or stabilization of intracellular signaling complexes (Figure 12A). KEGG enrichment analysis revealed that the key effector genes were primarily involved in the FcεRI signalling pathway, the platelet activation pathway, the osteoblast differentiation pathway, the phospholipase D signalling pathway, as well as processes related to senescence and lifespan regulation (Figure 12B).

Systematic bioinformatics analysis reveals that key effector genes of Phyllanthus emblica intervention in CVD are significantly enriched in multiple core biological processes and pathways, including immune-inflammatory regulation, reprogramming of energy metabolism, cellular signal transduction, and regulation of platelet function. These findings comprehensively delineate at the molecular level the networked pharmacological mechanism by which Phyllanthus emblica modulates immune homeostasis, improves metabolic disorders, and inhibits thrombosis through multi-targeted, multi-pathway synergistic actions. This not only deepens our understanding of the modern scientific basis for Phyllanthus emblica's traditional medicinal effects but also provides crucial theoretical foundations and directional guidance for subsequent experimental validation and precision drug interventions targeting key pathways (such as the FcεRI signaling pathway and platelet activation pathways).

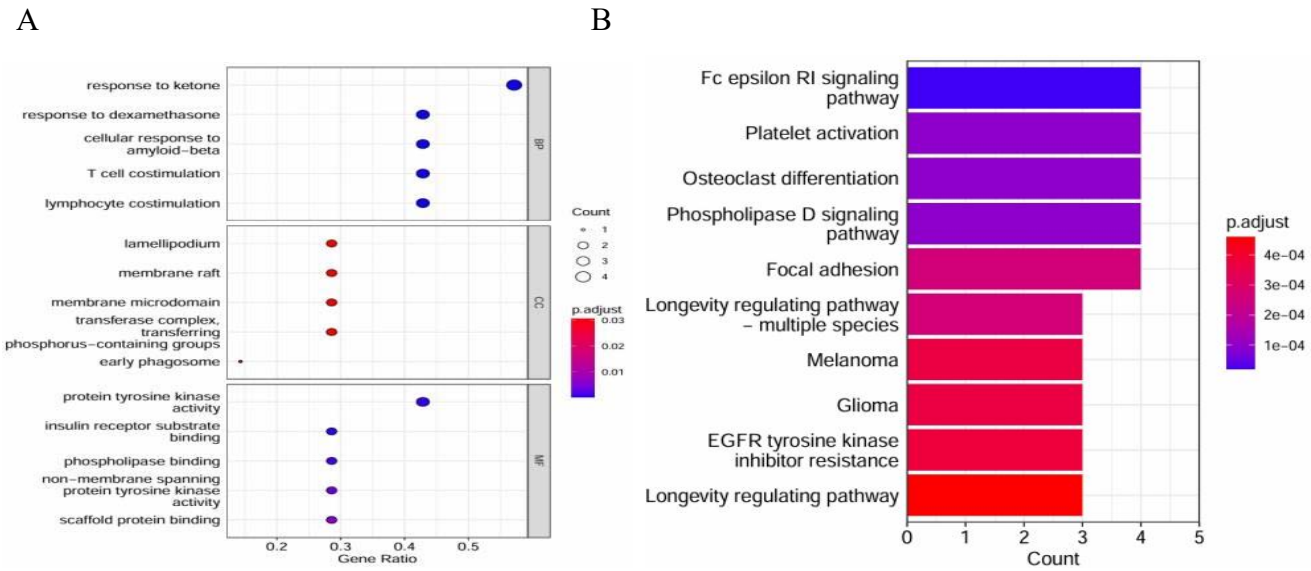

Figure 12. (A) GO enrichment analysis plot (B) KEGG enrichment analysis plot

3.11 Mendelian randomization analysis

Mendelian randomization analysis was used to verify the causal relationship between key effect genes and CVD. The causal effects between each key effector gene and CVD are shown in Figure 13.IVW analysis showed that AKT1 [OR=0.22,95% CI=(0.12,0.40), $P < 0.01$], FYN [OR=0.41,95% CI=(0.26,0.67), $P < 0.01$], IGF1R [OR=2.11,95% CI=(1.26,3.54), $P < 0.01$], SYK [OR=2.86,95%CI=(1.64,4.98), $P < 0.01$] four genes were causally associated with CVD, in which AKT1 and FYN genes were negatively associated with the disease. The IGF1R and SYK genes were positively associated with the disease, whereas the other three genes had no significant causal relationship. The causal effects of AKT1 on CVD are shown in Figures 14A–D. The causal effects of each genetic variant on CVD are shown in Figures 14A and B. In the IVW method analysis of the causal association between AKT1 and CVD, a negative correlation was found between AKT1 and CVD risk, with an OR of 0.22 (95% CI = (0.12, 0.40), $p < 0.01$). The MR-Egger method did not show statistical significance [OR = 0.83, 95% CI = 0.27–2.55, p = 0.74]. The causal effects in the funnel plot were roughly symmetric (Figure 14C), as confirmed by systematically performing MR analyses on the remaining SNPs, removing one SNP at a time in each analysis. The results remained consistent, indicating that

the causal effects were significant for all SNPs (Figure 14D) . The causal effects of FYN, IGF1R, and SYK on CVD are shown in Supplementary Materials Figure S8A–L.

Through Mendelian randomization analysis, this study genetically confirmed robust causal associations between four genes—AKT1, FYN, IGF1R, and SYK—and CVD. The analysis revealed that AKT1 and FYN exert significant protective effects, whereas IGF1R and SYK may act as risk factors promoting disease onset. This finding not only corroborates previous bioinformatics and machine learning-based screening results but also establishes the pivotal role of these genes in the onset and progression of CVD at the level of genetic causation.

The results highlight the potential value of these genes as therapeutic targets. Particularly, the protective effects demonstrated by AKT1 and FYN provide crucial genetic evidence and translational directions for developing precision therapies targeting these pathways. Furthermore, MR analysis demonstrated robust consistency and stability across multiple rounds of sensitivity testing, further enhancing the reliability of the conclusions. This study also provides novel research approaches and methodological insights for exploring the etiology of CVD and validating therapeutic targets.

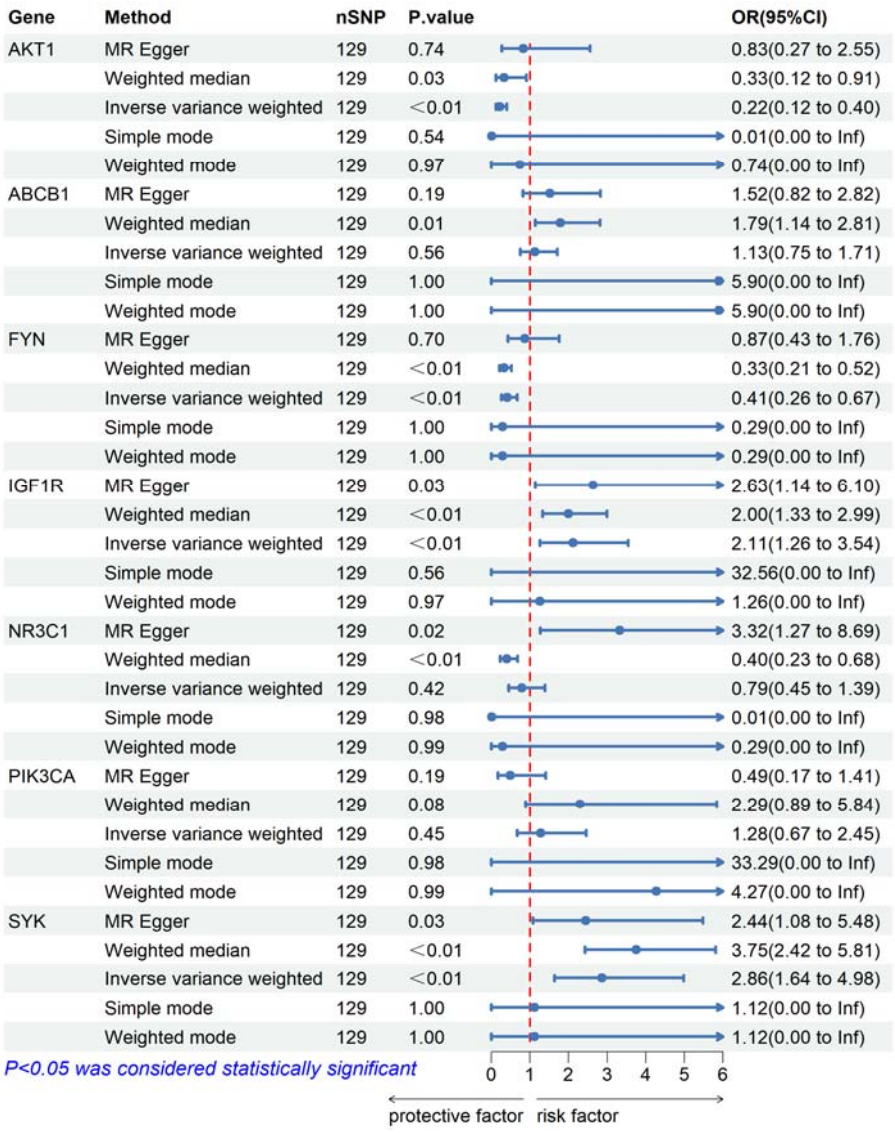

Figure 13. Forest plot of causal relationship between key effector genes and cardiovascular disease

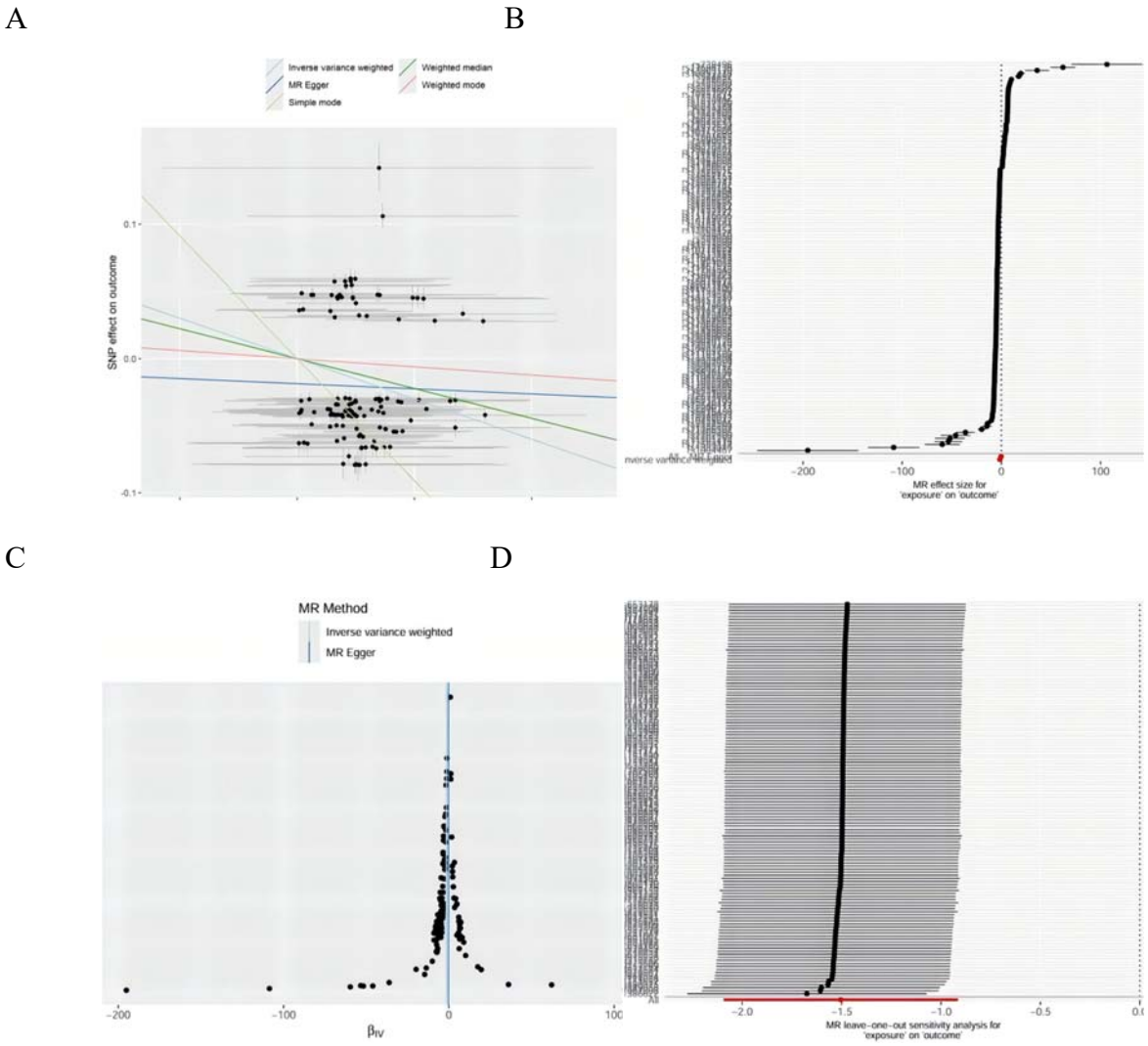

Figure 14. Mendelian randomization study results. (A) Scatter plot showing the causal effect of AKT1 on the risk of CVD. (B) Forest plot showing the causal effect of each SNP on the risk of CVD. (C) Funnel plots to visualize overall heterogeneity of MR estimates for the effect of AKT1 on CVD. (D) Leave-one-out plot to visualize causal effect of AKT1 on CVD risk when leaving one SNP out.

4. Discussion

CVD is one of the major causes of global health deterioration. According to the World Health Organization (WHO), CVD kills about 17.9 million people each year, accounting for 32% of all deaths. There are many risk factors for CVD, such as obesity, hypertension, dyslipidemia, and poor lifestyle habits, all of which increase the risk of the disease, and dyslipidemia has a significant impact on the development of CVD.

Studies have shown that dietary factors and healthy lifestyle behaviors can effectively prevent CVD. Therefore, developing functional foods with specific nutrients and implementing effective dietary interventions is essential for CVD prevention[31]. Phyllanthus emblica fruit has numerous uses, making it one of the more popular botanicals in the pharmaceutical, culinary, and cosmetic industries[32]. In various animal and human studies, Phyllanthus emblica has been shown to possess antihyperglycemic, hypoglycemic, anti-inflammatory, antihyperlipidemic, and antioxidant activities. In a study by Lin et al.[33], the antidiabetic and antihyperlipidemic activities, as well as the molecular mechanisms, of Phyllanthus emblica extract in high-fat-fed mice were investigated. The study showed a significant reduction in TG and TC levels in the

blood of mice treated with Phyllanthus emblica extract. Similarly, in a population study by Gopa et al.[34], it was found that after 42 days of treatment with Phyllanthus emblica extract capsules, the mean levels of TC, LDL, VLDL, and TG were significantly reduced, while HDL levels were significantly increased in hyperlipidemic patients. Based on previous studies and the relationship between Phyllanthus emblica and CVD, we explored the mechanism of the effect of Phyllanthus emblica on CVD by meta-analysis combined with network pharmacology and Mendelian randomization analysis.

The meta-analysis showed that intervention with Phyllanthus emblica significantly reduced TC, LDL, VLDL, and TG levels and increased HDL levels. It also decreased MDA and hsCRP levels and increased NO and GSH levels in patients with CVD. The results generally agreed with the findings of Bhatia et al[35]. Subsequently, we investigated the specific functional constituents of Phyllanthus emblica and identified four functional constituents after excluding those with toxic effects: ellagic acid, kaempferol, luteolin, and phyllanthin. Ellagic acid is a natural polyphenolic compound found in various plants, including grapes, pomegranates, and nuts. It has been found that ellagic acid exhibits anti-inflammatory, antioxidant, anti-allergic, and ischemia-reperfusion injury effects, in addition to its antitumor properties[36]. In a study by Altamimi et al.[37], it was found that ellagic acid significantly reduced liver and serum levels of TG, TC, and free fatty acids in diabetic rats and exerted hypolipidemic effects in an AMPK-dependent manner.

Meanwhile, Kannan et al.[38] found that oral pretreatment with ellagic acid restored pathologic arrhythmias, ventricular hypertrophy, lipid peroxidation, an altered lipid profile, and myocardial necrosis in isoprenaline-induced myocardial infarction rats. Its anti-lipid peroxidation property of inhibiting 3-hydroxy-3-methyl glutaryl CoA reductase inhibition and anti-hyperlipidemic activity may be responsible for the beneficial effects on the amelioration of myocardial infarction. Other studies have shown that, as an anti-inflammatory agent, ellagic acid may also help increase the function of VEGF in endothelial cells and accelerate the angiogenesis process[39]. Fruit and vegetable intake has been associated with a reduced risk of CVD, and kaempferol is one of the most prevalent polyphenols found in fruits and vegetables[40]. In *in vitro* studies, kaempferol has been shown to have antioxidant and anti-inflammatory effects, and its potential cardioprotective effects may derive from its anti-inflammatory activity[41-43]. In a study by Feng et al.[44], kaempferol, following intervention, was shown to be protective against atherosclerosis in postmenopausal mice. In de-ovulated mice fed a high-fat diet, kaempferol improved vascular morphology, normalized lipid levels, and significantly suppressed the overproduction of ROS, inflammation, and apoptosis before administration. Luteolin is abundantly found in the plant kingdom, primarily in medicinal plants such as honeysuckle, Scutellaria, and dandelion, as well as in crops like peanut shells and corn husks. Luteolin is used in the treatment of various diseases due to its rich pharmacological effects and remarkable medicinal value, and its pharmacological properties have been demonstrated in several studies [45]. In a study by Wei et al[46], luteolin was found to exert significant cardioprotective effects *in vivo* and *in vitro* by improving cardiac function, increasing the expression of the anti-apoptotic protein Bcl-2, and decreasing the expression of the pro-apoptotic proteins Bax and active caspases 3 and 9, which are associated with myocardial

ischemia/reperfusion (MI/R) injury *in vivo*. In addition, luteolin is beneficial *in vitro* and *in vivo* against dysfunctional glucose-lipid metabolism, effectively inhibiting cellular cholesterol synthesis[47]. Phyllanthin is a natural compound with various biological properties, including antioxidant, hepatoprotective, anticancer, anti-inflammatory, and antihyperglycemic activities. There are relatively few studies on the hypolipidemic and cardiovascular protective effects of Phyllanthin, so more in-depth research on this substance is still needed.

In this study, we utilized the relationship between Phyllanthus emblica and CVD by selecting a dataset from a study on familial hypercholesterolemia in the GEO database to refine the selection of target genes associated with CVD. A combination of differential analysis, WGCNA analysis, and machine learning algorithms was used to identify disease genes from a gene database, resulting in seven cardiovascular-related target genes: AKT1, ABCB1, FYN, IGF1R, NR3C1, PIK3CA, and SYK. AKT1 is a serine/threonine kinase that plays a key role in intracellular signalling. It is widely found in various tissues and cell types and is a core component of the PI3K/AKT signalling pathway. In a study by Ha et al.[48], AKT1 isoforms were found to play a crucial role in vascular smooth muscle cells.AKT1 enhances vascular maturation by up-regulating angiopoietin 1 (Ang1) through activation of the Notch signalling pathway (Notch3) and down-regulating angiopoietin 2 (Ang2) through inhibition of Yes-associated protein (YAP) transcriptional activity.

Additionally, AKT1 plays a crucial role in regulating cell growth and glucose metabolism [49]. ABCB1, or MDR1, is a member of the ATP-binding cassette (ABC) family of transporter proteins[50]. The ATP-binding cassette (ABC) family of transporter proteins plays a vital role in depositing pathological peptides in neurodegenerative diseases. It has been found that ABCB1 is commonly expressed in endothelial cells of the microvascular system and in a subset of larger vessels (mainly small veins) in brain regions where the blood-brain barrier (BBB) has been established[51]. ABCB1 also encodes the P-glycoprotein (P-gp), which determines the concentration of drugs reaching the target tissue, of which statins are one of the substrates, and which are commonly used for primary and secondary prevention of coronary heart disease[52,53]. FYN is a non-receptor tyrosine kinase that participates in various membrane receptor-initiated cytoplasmic signaling cascades and has been shown to maintain cardiac homeostasis by negatively regulating NOX4 activity and optimizing ROS production in cardiomyocytes[54,55]. IGF1R, the insulin-like growth factor 1 receptor, is a crucial transmembrane tyrosine kinase receptor that plays a pivotal role in various physiological processes, including cell growth, differentiation, metabolism, and survival. It has been shown that IGF1R has a dual biphasic effect on cardiac health. That inhibition of IGF1R signalling by dominant-negative phosphatidylinositol 3-kinase (PI3K) mutants induces cardioprotective autophagy, which restores myocardial bioenergetics and improves late-life survival[56].

Meanwhile, a study by Abdellatif et al.[57] found that young mice with increased IGF1R signalling exhibited superior cardiac function compared to wild-type mice. Still, this function declined at an accelerated rate with age, leading to heart failure and shortened lifespan. In contrast, mice with low cardiac IGF1R signalling exhibited poor cardiac function early in life but showed excellent cardiac function during ageing

and an increased maximum lifespan. NR3C1 is the gene encoding the glucocorticoid receptor (GR), and related studies have shown that mice lacking GR develop symptoms such as cardiac hypertrophy and left ventricular systolic dysfunction. Meanwhile, physiological GR signalling exerts a protective effect by acting locally within myofibers and cardiomyocytes to protect tissues from dystrophic disease processes[58, 59]. PIK3CA may play a key role in regulating iron death during the progression of acute myocardial infarction, as shown in reports on PIK3CA[60]. SYK is a 72 kDa non-receptor tyrosine kinase, and studies have shown that it is associated with atherosclerosis, stroke, heart failure, diabetic cardiomyopathy, and various other diseases[61]. Several SYK inhibitors have been developed clinically and have shown preliminary effects on slowing the progression of pathological diseases. Inhibition of SYK may also slow the progression of activated macrophage-mediated atherosclerosis[62-64]. Together, these studies suggest that AKT1, ABCB1, FYN, IGF1R, NR3C1, PIK3CA, and SYK may serve as potential biomarkers for CVD and play a key role in the disease's pathophysiology.

In this study, we also explored the roles and potential mechanisms between key effector genes and functional components of Phyllanthus emblica through molecular docking. The results showed that the functional components formed stable complexes with the key effector genes mainly through hydrogen bonding. The binding energies of all docking combinations were less than -4.0 kcal/mol. These results suggest that the functional components of Phyllanthus emblica may interact with key effector genes, exerting cardiovascular ameliorative effects through these genes. In addition, key effector genes were found to be involved in the FcεRI signalling pathway, platelet activation pathway, phospholipase D signalling pathway, as well as ageing and lifespan regulatory processes, as determined by pathway enrichment analysis. These pathways play essential roles in inflammatory responses, thrombosis, lipid metabolism, chronic inflammation, and tissue injury. These organismal changes are important pathological mechanisms of CVD, which in turn contribute to the onset of CVD. To further validate the relationship between key effector genes and CVD, a Mendelian randomization analysis was conducted in this study, revealing a significant causal relationship between the AKT1, FYN, IGF1R, and SYK genes and CVD. This result further confirmed our hypothesis.

Research on the functional components and gene targets of Phyllanthus emblica offers novel insights for CVD treatment. As a substance with dual medicinal and dietary properties, it possesses high nutritional value, which warrants its broader clinical application. Mendelian randomization results suggest that IGF1R and SYK may act as risk factors for disease onset, indicating a potential for developing specific inhibitors targeting these two pathways. Research indicates that IGF1R exhibits dual roles in the cardiovascular system, both protective and detrimental. It promotes the proliferation and migration of vascular smooth muscle cells, contributing to the formation of atherosclerotic plaques. Concurrently, hyperglycemia and insulin resistance often co-occur with abnormalities in the IGF-1R signaling pathway. Such dysregulation may exacerbate vascular endothelial dysfunction, inflammation, and oxidative stress, thereby significantly increasing the risk of CVD. The role of SYK *in vivo* is relatively more defined. It primarily functions as a core mediator of pro-inflammatory and immune responses, playing a clear role as a "risk factor" or "driver" in inflammatory

CVD such as atherosclerosis. Molecular docking results revealed strong binding interactions between ellagic acid, kaempferol, and luteolin—functional components of Phyllanthus emblica—and IGF1R, while kaempferol and luteolin exhibited strong binding with SYK. Therefore, kaempferol and luteolin extracts from Phyllanthus emblica can be validated using *in vitro* cell models and *in vivo* animal models. Subsequently, these functional components should undergo standardization and quality control before being subjected to small-scale population trials for validation. Combining multi-omics technologies, dynamically monitor changes in patients' immune-inflammatory markers, lipid metabolism pathways, and platelet function post-medication to validate potential mechanisms of action.

With the advancement of genetic engineering technology, genetic testing can analyze specific genotypes in patients with CVD (such as high expression of IGF1R and SYK), thereby identifying populations most likely to respond to Phyllanthus emblica therapy. This strategy facilitates personalized medication and promotes the clinical application of precision nutrition and precision Chinese herbal interventions. Notably, the mechanisms of action for single functional components often exhibit limitations. Therefore, combining key bioactive constituents in Phyllanthus emblica (such as kaempferol and luteolin) with existing cardiovascular medications for systematic evaluation of synergistic potential should be considered. Through multi-targeted, multi-pathway synergistic regulation, this approach not only holds promise for enhancing therapeutic efficacy but may also mitigate adverse reactions associated with certain drugs, offering novel insights for treating complex cardiovascular conditions.

Integrating the functional components of Phyllanthus emblica with relevant targets for CVD and ultimately achieving clinical translation constitutes a complex and systematic endeavor that requires long-term investment and commitment. This process heavily relies on interdisciplinary collaboration, necessitating the integration of expertise from molecular biology, network pharmacology, clinical medicine, and other fields to collectively advance the transition from traditional empirical medicine to modern evidence-based therapies. Given Phyllanthus emblica's dual status as both food and medicine, functional foods or dietary supplements offer a priority entry point for its benefits. After accumulating sufficient human efficacy data and mechanism evidence, development can progress toward advanced health products with explicit functional claims, or even novel plant-based drugs. The ultimate goal is to establish Phyllanthus emblica as an evidence-based adjunctive treatment for CVD, thereby providing patients with safer, more personalized, and integrated healthcare options.

Phyllanthus emblica is widely distributed across South and Southeast Asia, including India, Sri Lanka, and the Philippines, leading to concentrated research on its applications in these regions. Our analysis revealed that many CVD-related studies originated from India, potentially introducing geographical bias. However, numerous studies have investigated its diverse therapeutic properties beyond regional limitations. Li et al[65] detailed the effects of Phyllanthus emblica on oral health, noting that in traditional Chinese medicine (TCM), this herb is believed to nourish yin, reduce pathogenic fire, and alleviate dryness. These properties make it particularly effective in relieving throat discomfort and stimulating saliva production in individuals with

diabetes. Lu et al[66] demonstrated through *in vitro* studies that Phyllanthus emblica extract exhibits potent anti-inflammatory activity against sexually transmitted infection-associated pathogens. Subsequent randomized controlled trials revealed that a Phyllanthus emblica-based mouthwash significantly reduced volatile sulfur compound (VSC) levels in the oral cavity at 3-, 6-, and 12-hour post-rinsing intervals compared to placebo controls ($P < 0.05$). These findings confirm its dual therapeutic mechanism involving antibacterial action and malodor mitigation. Since the initiation of the National Cancer Institute (NCI) screening program, over 110,000 plant-derived extracts and purified compounds have been evaluated for their anticancer potential. Extensive research has demonstrated that Phyllanthus emblica exhibits multiple pharmacological activities, including anti-inflammatory, antibacterial, and antioxidant properties. Furthermore, through various mechanisms, preclinical studies have revealed its neuroprotective effects, hepatoprotective and cardioprotective capacities, as well as its chemopreventive potential[67]. In addition, Luo et al[68] demonstrated that the aqueous extract of Phyllanthus emblica significantly reversed gut microbiota dysbiosis in a murine model of non-alcoholic fatty liver disease (NAFLD) with progressive liver fibrosis. The treatment restored microbial diversity to normal levels and normalized the composition of specific bacterial taxa, suggesting its therapeutic potential for NAFLD through microbiota modulation. Although Phyllanthus emblica is primarily cultivated in specific geographical regions, its phytochemical constituents and health benefits have been extensively investigated. Owing to its rich nutritional profile and status as a medicinal food, future research should analyze its active ingredients and expand its application in functional foods and medicines to benefit more people worldwide.

This study demonstrates that Phyllanthus emblica possesses significant efficacy in ameliorating CVD and delaying its progression, primarily through the regulation of blood lipids. The underlying mechanism is likely mediated by the interactions of its functional components with key targets, including AKT1, ABCB1, FYN, IGF1R, NR3C1, PIK3CA, and SYK. Consequently, Phyllanthus emblica and its active constituents represent promising candidates for developing therapeutic strategies to alleviate adverse symptoms in patients with CVD.

Supplementary materials

Supplementary materials include：

Figure S1 Cochrane Collaboration Tool Quality Assessment Chart.

Figure S2 Intervention duration subgroup analysis chart (A) TG subgroup analysis (B) TC subgroup analysis (C) LDL subgroup analysis (D) HDL subgroup analysis (E) VLDL subgroup analysis.

Figure S3 Intervention dose subgroup analysis chart (A) TG subgroup analysis (B) TC subgroup analysis (C) LDL subgroup analysis (D) HDL subgroup analysis (E) VLDL subgroup analysis.

Figure S4 Sensitivity analysis chart (A) TG sensitivity analysis chart (B) TC sensitivity analysis chart (C) LDL sensitivity analysis chart (D) HDL sensitivity analysis chart (E) VLDL sensitivity analysis chart.

Figure S5 Publication bias funnel plot (A) TG publication bias funnel plot (B) TC publication bias funnel plot (C) LDL publication bias funnel plot (D) HDL publication bias funnel plot (E) VLDL publication bias funnel plot.

Figure S6 (A) FYN box plot (B) SYK box plot (C) ABCB1 box plot (D)IGF1R box plot (E) NR3C1 box plot (F) PIK3CA box plot.

Figure S7 (A) Docking diagram of AKT1-EllagicAcid molecule (B) Docking diagram of AKT1-kaempferol molecule (C) Docking diagram of AKT1-luteolin molecule (D) Docking diagram of AKT1-Phyllanthin molecule (E) Docking diagram of ABCB1-kaempferol molecule (F) Docking diagram of ABCB1- luteolin molecule (G) Docking diagram of FYN-Ellagic Acid molecule (H) Docking diagram of IGF1R-kaempferol molecule (I) Docking diagram of IGF1R-luteolin molecule (J) Docking diagram of IGF1R-Phyllanthin molecule (K) Docking diagram of NR3C1-Phyllanthin molecule (L) Docking diagram of SYK-kaempferol molecule.

Figure S8 Mendelian randomization study results. (A) Scatter plot showing the causal effect of FYN on the risk of CVD. (B) Forest plot showing the causal effect of each SNP on the risk of CVD. (C) Funnel plots to visualize overall heterogeneity of MR estimates for the effect of FYN on CVD. (D) Leave-one-out plot to visualize causal effect of FYN on CVD risk when leaving one SNP out. (E) Scatter plot showing the causal effect of IGF1R on the risk of CVD. (F) Forest plot showing the causal effect of each SNP on the risk of CVD. (G) Funnel plots to visualize overall heterogeneity of MR estimates for the effect of IGF1R on CVD. (H) Leave-one-out plot to visualize causal effect of IGF1R on CVD risk when leaving one SNP out. (I) Scatter plot showing the causal effect of SYK on the risk of CVD. (J) Forest plot showing the causal effect of each SNP on the risk of CVD. (K) Funnel plots to visualize overall heterogeneity of MR estimates for the effect of SYK on CVD. (L) Leave-one-out plot to visualize causal effect of SYK on CVD risk when leaving one SNP out.

Table S1 Modified Jadad scoring scale.

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Declaration of Competing Interest

The authors declare no competing interest.

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