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Exploring the mechanism of fibrates regulating HIF-1A in the treatment of ischemic stroke based on network pharmacology and molecular docking

Fengjiao Yang[1,5†], Zixuan Yang[5†], Ya Yan[2], Yun Gu[3], Pengyu Wang[1], Min Wang[1], Jianjie Chen[1], Xiaoshan Du[4] and Guangming Wang[1*]

Abstract

Fibrates can prevent and treat ischemic stroke (IS), the occurrence and development of IS is closely related to hypoxia-inducible factor-1A (HIF-1A). However, the exact mechanism by which fibrates regulate HIF-1A to treat IS remains unclear. So network pharmacology and molecular docking were used to explore the mechanism by which fibrates regulate HIF-1A to treat IS, firstly, the structure of five fibrates were obtained by reviewing the literature and pharmacopoeia, then the potential targets of fibrates, IS, HIF1A and HIF1A-related genes were obtained through various databases, their common targets were obtained through Venny 2.1.0. The PPI network diagram of fibrates, IS and HIF1A-related genes was plotted by String and Cytoscape3.8.1. The GO functional analysis results and KEGG pathways of fibrates, IS, HIF1A and HIF1A related genes were obtained by Metascape. Finally, the molecular docking of fibrates and HIF1A was performed by AutoDock. The common targets of five fibrates and IS showed that only 3 fibrates contained HIF1A, GO functional analysis, KEGG pathway analysis and molecular docking showed that fibrates can better regulate HIF1A to treat IS, its main action pathways are pathways in cancer, lipid and atherosclerosis and HIF-1 signaling pathway.

Keywords Fibrates, IS, HIF1A, Network pharmacology, Molecular docking

Introduction

In recent years, the establishment of stroke centers has made stroke patients get more effective treatment, but the incidence of stroke still shows an increasing trend [1]. IS accounts for about 80% of stroke [2]. At present, thrombolysis and mechanical thrombectomy are the most effective methods for IS [3], but mechanical thrombectomy may lead to bleeding, which will further aggravate brain damage. Therefore, thrombolytic drugs are often used to treat IS, but thrombolytic therapy must be administered within 4.5 h after the onset of IS, which often results in many patients not receiving effective treatment [4]. Therefore, some anti-platelet drugs,

†The contributions of Fengjiao Yang and Zixuan Yang are the same in this study.

*Correspondence:
Guangming Wang
wgm1991@dali.edu.cn
[1] College of Clinical Medicine, Dali University, Dali 671000, Yunnan, People's Republic of China
[2] College of Pharmacy, Dali University, Dali 671000, Yunnan, People's Republic of China
[3] Department of Pharmacy, The First Affiliated Hospital of Dali University, Dali 671000, Yunnan, People's Republic of China
[4] Department of Geriatrics, South District of Hefei First People's Hospital, Hefei 230000, Anhui, People's Republic of China
[5] Department of Pharmacy, The People's Hospital of Baoshan, Baoshan 678000, Yunnan, People's Republic of China

anti-coagulants and neuroprotective drugs are commonly used to prevent and treat IS.

The rising incidence of IS has imposed a considerable economic burden on society and the families of patients [5, 6]. Therefore, the effective prevention of IS is important to improving people's quality of life. Effective intervention the high risk factors of IS is the most effective and fundamental measure to reduce the occurrence of IS. Blood lipid levels are closely related to the occurrence risk of IS [7], when blood lipid levels are abnormal, the early use of lipid-lowering drugs can effectively prevent the occurrence of IS [8]. Fibrates belongs to the lipid-lowering drugs of phenoxyaromatic acid class, it can enhance lipoprotein esterase activity, accelerate proteolysis, reduce lipoprotein synthesis, lower low-density lipoproteins and triglycerides, elevate high-density lipoproteins, which can prevent blood clotting and promoting thrombolysis, which may effectively reduce the occurrence risk of IS [9, 10]. Fenofibrate, clofibrate, bezafibrate and gemfibrozil are the most commonly used fibrates in clinical practice (Fig. 1). Pirinic acid has not been used in clinical practice, but its lipid-lowering effect has been widely studied in the laboratory (Fig. 1).

The pathogenesis of IS is complex, which is often causes various reactions such as energy metabolism disorders, oxidative stress, inflammatory response and neuronal damage [11, 12]. Network pharmacology emphasizes the analysis of the relationship among drugs, genes and diseases from the systemic level and the overall perspective of biological network, its integrity and systematization are consistent with the complex pathogenesis of diseases. So the methods of network pharmacology and molecular docking were used to illustrate the mechanism by which fibrates regulate HIF1A to prevent and treat IS (Fig. 2). We hope that this study can provide some reference for the follow-up study of fibrates regulating HIF1A to prevent and treat IS.

Materials and methods

Targets screening of fibrates

The chemical structures of "fenofibrate, pirinixic acid, clofibrate, bezafibrate, and gemfibrozil" were imported into the Swiss Target Prediction (http://www.swisstargetprediction.ch/) [13], "Homo sapiens" was selected as the species, finally, the targets of five fibrates could be obtained. Then "fenofibrate, pirinixic acid, clofibrate, bezafibrate, and gemfibrozil" were imported into the CTD (http://ctdbase.org/) [14], the "Gene" was selected, finally, the targets of 5 fibrates could be obtained. After all targets are obtained, the duplicate targets were removed, lastly, the final targets of each drug was obtained.

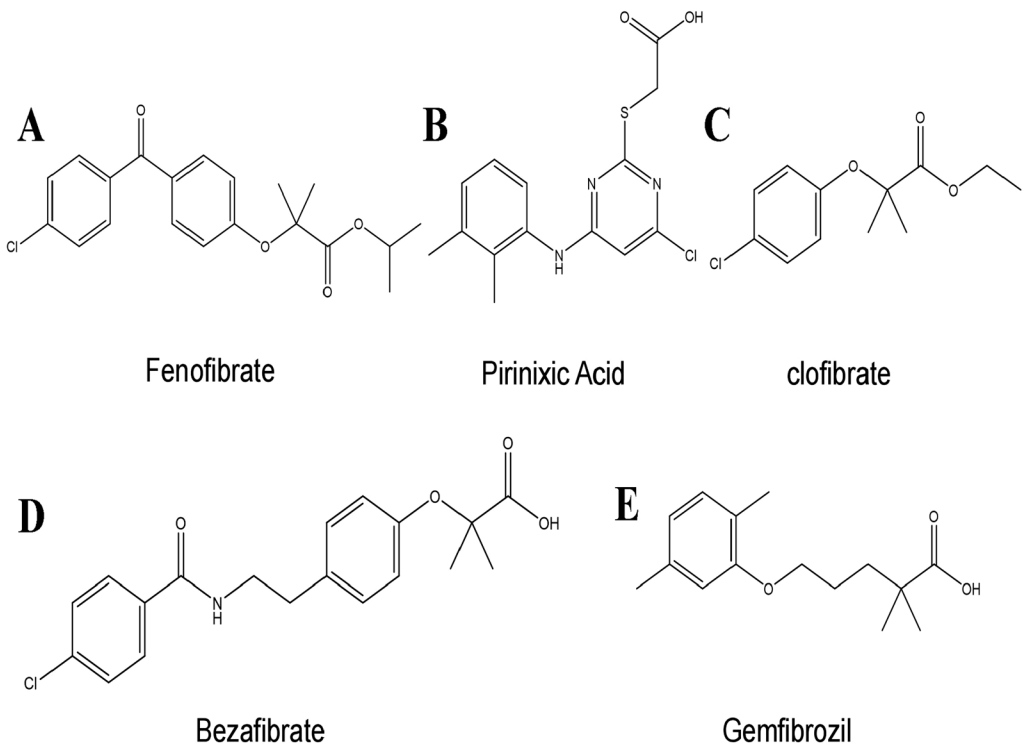

Fig. 1 Chemical structure of fibrates. **A** Fenofibrate; **B** pirinixic acid; **C** clofibrate; **D** bezafibrate; **E** gemfibrozil

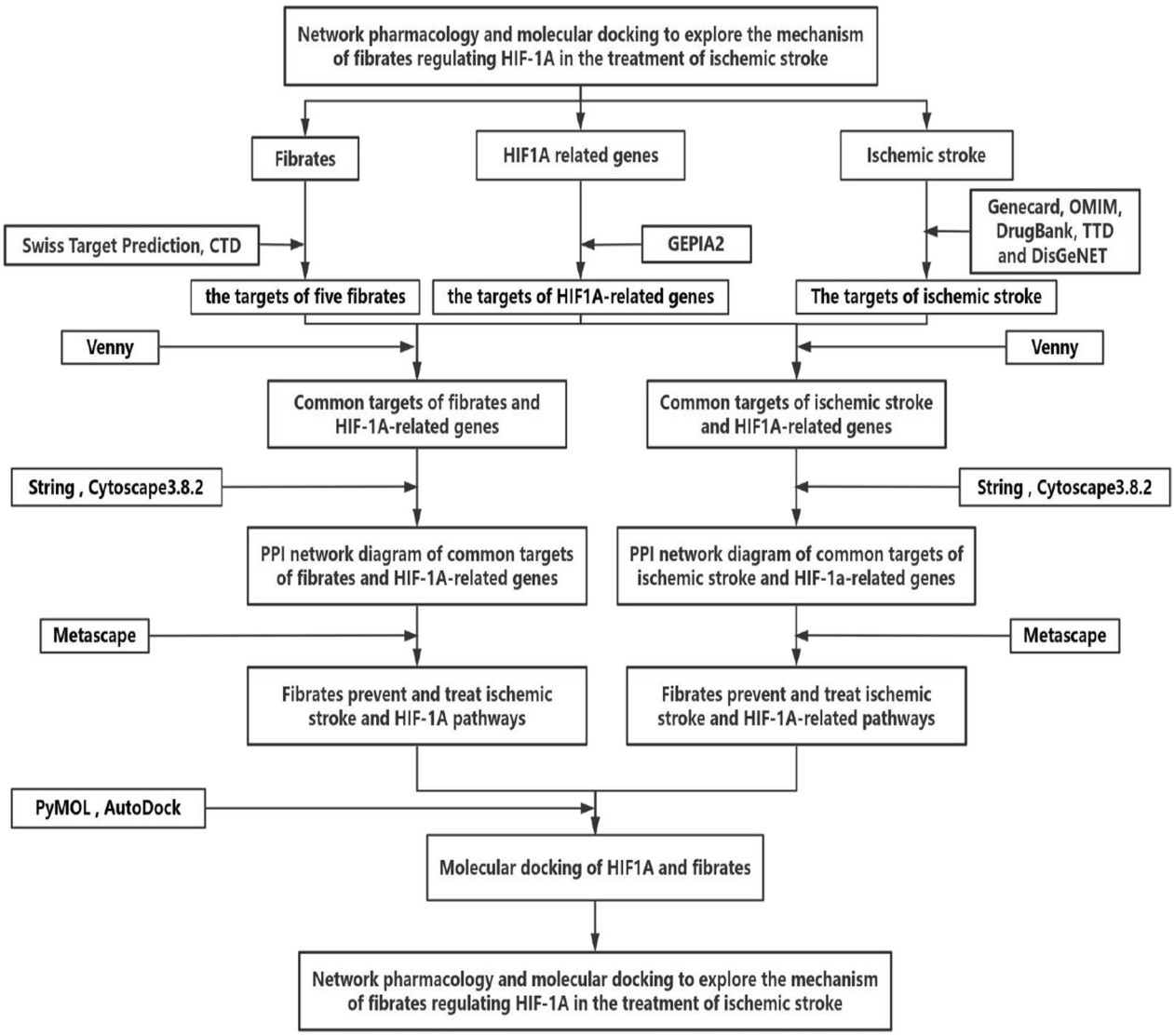

Fig. 2 The flow chart of this study

Targets screening of IS

"Ischemic stroke" was used as the search term, then targets of IS was obtained through Genecard (https://www.genecards.org/) [15], OMIM (https://omim.org/) [16], DrugBank (https://www.drugbank.com/) [17], TTD (https://db.idrblab.net/ttd/) [18] and DisGeNET (https://www.disgenet.org/) [19], the obtained targets were summarized, then duplicated targets were removed to obtain the final targets of IS.

Common targets of fibrates and IS

The targets of fibrates and IS were imported into the Venny 2.1.0 (https://bioinfogp.cnb.csic.es/tools/venny/) [17], then common targets of fibrates and IS were obtained.

The screening of HIF1A-related genes, the screening of common targets of HIF1A-related genes and fibrates

"HIF1A" was imported into GEPIA2 (http://gepia2.cancer-pku.cn/) [20], then the targets of HIF1A-related genes could be obtained. Finally, common targets of fibrates and HIF1A-related genes were obtained through the Venny 2.1.0.

PPI network diagram of the common targets of fibrates and IS

The common targets of fibrates and IS were imported into the String (https://string-db.org/) [21], select medium reliability (0.400), disconnected nodes are hidden, then the PPI network data sheet is exported. The PPI network data sheets were import into Cytoscape3.8.2, degree,

intermediate centrality and proximity centrality were calculated, then the core targets were filtered by above parameters, finally, the PPI network diagram of fibrates and IS were obtained. In PPI networks, nodes represent targets, lines represent the relationship between targets and targets.

PPI network diagram of the common targets of fenofibrate, pirinixic acid, clofibrate and HIF1A-related genes

The common targets of fenofibrate, pirinixic acid, clofibrate and HIF1A-related genes were imported into the String, select medium reliability (0.400), disconnected nodes are hidden, then the PPI network data sheet is exported. The data sheet were import into Cytoscape3.8.2, then the PPI network diagram of fenofibrate, pirinixic acid, clofibrate and HIF1A related genes were obtained.

Enrichment analysis of common targets of fibrates and IS

GO functional analysis and KEGG pathway analysis can systematically analyze the function of genes from the perspective of gene and molecular network, so KEGG has become a reference resource for genome decoding [22–24]. In order to further clarify the related functions and pathways of fibrates regulating HIF1A therapy for IS, GO functional analysis and KEGG pathway analysis were performed by the Metascape (http://www.metascape.org/) [25]. The common genes of fibrates and IS are imported Metascape, "Homo sapiens" was selected as the species, then "Custom Analysis" was selected, finally, GO and KEGG analyses were performed. The GO functional analysis result and KEGG analysis result of fibrates and IS were obtained, then the GO enrichement term diagram and KEGG pathways bubble diagram was plotted by the bio-informatics platform, it could explore the mechanism by which fibrates regulate HIF-1A to prevent and treat IS.

Enrichment analysis of common targets of fibrates and HIF1A-related genes

The common gene sets of fenofibrate, pirinixic acid, clofibrate and HIF1A-related genes are imported Metascape, then GO functional analysis and KEGG analysis was performed. Finally, the GO functional analysis result and KEGG analysis result of pirinixic acid, clofibrate and HIF1A-related genes were obtained, then the GO enrichement term diagram and KEGG pathways bubble diagram was plotted, which could explore the relationship of fibrates and HIF1A-related genes.

Molecular docking of HIF1A and fibrates

HIF1A was imported into the Uniprot (https://www.uniprot.org/) [26], reviewed (Swiss-Prot) was selected as status, human was selected as popular organisms, then HIF1A protein receptors were identified (Q16665 HIF1A HUMAN). The protein receptor of HIF1A was imported into the PDB, "homo sapiens" was selected as scientific name of source organism, refinement resolution (Å) as small as possible, more small molecule ligand information was included, finally, the HIF-1A receptor protein sequence was obtained (6GMR). The 3D chemical structures of fenofibrate, pirinixic acid and clofibrate were obtained by relevant software. The water molecules of HIF1A receptor protein and drug active components were removed by PyMOL-2.5.7, then the HIF1A receptor protein was imported into AutoDock-4.2.6 to perform hydrogenation and calculated charge. The docking pocket and docking parameters were set in AutoDock Vina-1.2.3, then the molecular docking of fibrates and HIF1A was performed.

Results

Screening of relevant targets

Gene sets of fibrates

The targets of five fibrates were collected through the Swiss Target Prediction and CTD, which is shown in Table 1. The results show that the targets number of pirinixic acid is the most, the targets number of gemfilozil is the least.

Table 1 The targets number of 5 fibrates

Fibrates	Swiss Target Prediction	CTD	Total number of targets	The number of repeated targets	The final number of targets
Fenofibrate	100	763	863	16	847
Pirinixic acid	100	7642	7742	59	7683
Clofibrate	100	3133	3233	30	3203
Bezafibrate	100	249	349	9	340
Gemfibrozil	100	104	204	6	199

Gene sets of IS

3041 targets of IS were collected in the Genecard, 129 targets of IS were collected in the OMIM, 0 targets of IS were collected in the TTD, 15 targets of IS were collected in the DisGeNET. 61 targets of IS were collected in DrukBank, a total of 3246 targets were obtained, 69 duplicated targets were removed, finally, 3177 targets were obtained.

Common gene sets of fibrates and IS

The Venn diagram of fibrates and IS was obtained (Fig. 3), which is shown that the common targets of pirinixic acid and IS is the most, which has 1119. The common targets of gemfibrozil and IS is the lowest, which has 91.

Common gene sets of HIF1A-related genes and fibrates

The gene set of HIF1A-related genes was obtained, which has 100, the Venn diagram of HIF1A-related genes and fibrates was obtained through the Venny 2.1.0 (Fig. 4). The results showed that the common targets of HIF1A-related genes and pirinixic acid is the most, which has 43, the common targets of HIF1A-related genes and gemfibrozil is the least, which has 1.

The PPI network diagram of fibrates and IS

The PPI network diagram of the common gene sets of fibrates and IS were constructed (Fig. 5). The results show that fibrates and IS have more edges and nodes in the PPI network diagram, therefore, fibrates are a good adjuvant drug for IS.

The PPI network diagram of fibrates and HIF1A-related genes

The PPI network diagram of the common gene sets of fenofibrate, pirinixic acid, clofibrate and HIF1A-related genes were constructed (Fig. 6). The results showed that the correlation of fenofibrate and HIF1A-related genes was weak, the PPI network diagram of their common genes had 3 nodes and 2 edges. There was a strong correlation between pirinixic acid and HIF1A-related genes, the PPI network diagram of their common genes had 30 nodes and 37 edges. Bezafibrate and gemfibrozil do not contain HIF1A and the above two drugs and HIF1A-related genes have only a few common targets, they may regulate other targets to treat IS, so their PPI network diagrams are not shown.

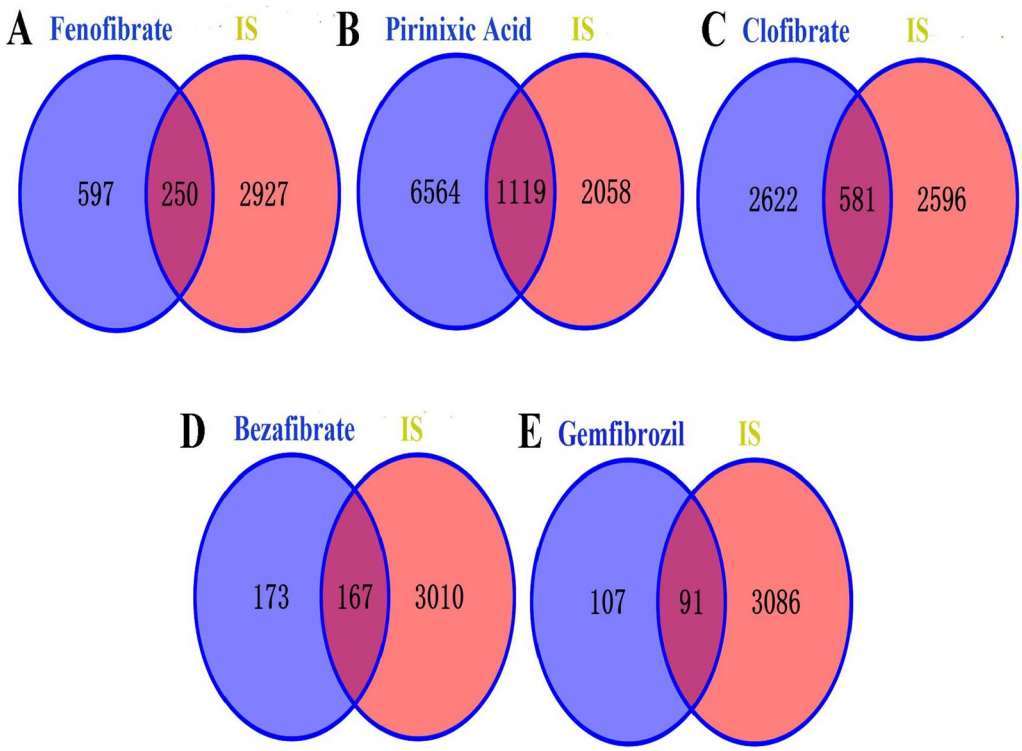

Fig. 3 Venn diagram of common targets of fibrates and IS. **A** Venn diagram of common targets of fenofibrate and IS; **B** Venn diagram of the common targets of pirinixic acid and IS; **C** Venn diagram of the common targets of clofibrate and IS; **D** Venn diagram of the common targets of bezafibrate and IS; **E** Venn diagram of common targets of gemfibrozil and IS

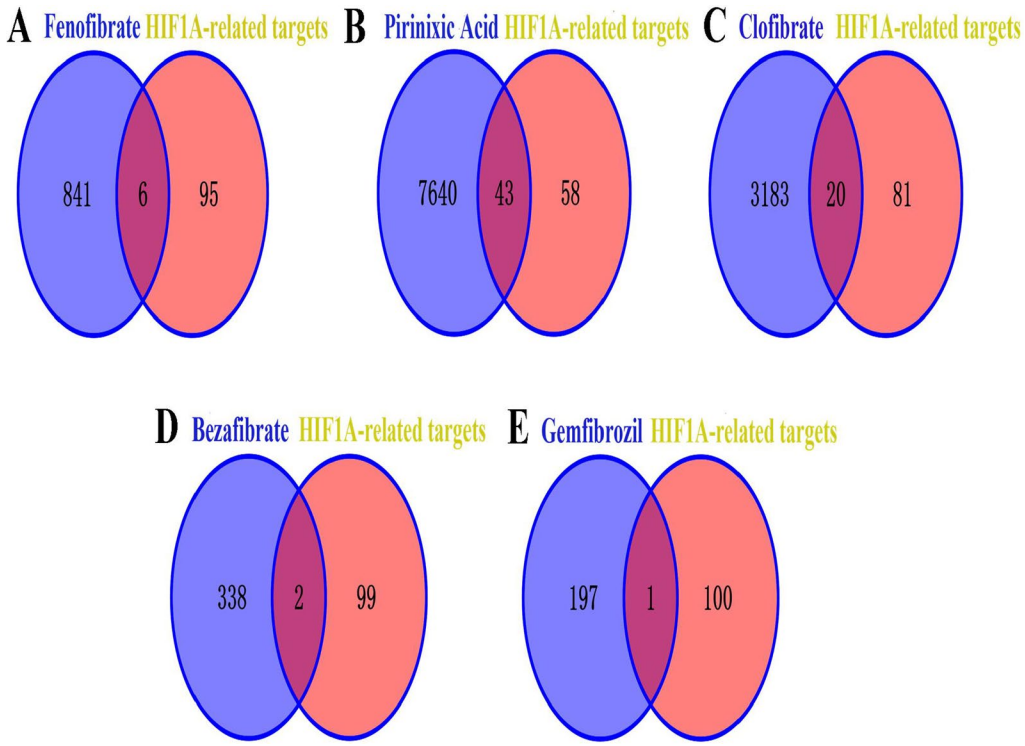

Fig. 4 Venn diagram of common targets of fibrates and HIF1A-related genes. **A** Venn diagram of common targets of fenofibrate and HIF1A-related genes; **B** Venn diagram of common targets of pirinixic acid and HIF1A-related genes; **C** Venn diagram of common targets of clofibrate and HIF1A-related genes: **D** Venn diagram of common targets of bezafibrate and HIF1A-related genes; **E** Venn diagram of common targets of gemfibrozil and HIF1A-related genes

GO functional analysis and KEGG enrichment analysis of fibrates treat IS

GO functional and KEGG pathways of fibrates treat IS were analyzed (Figs. 7 and 8). GO function analysis showed that the GO Biological Processes is main associated with hormonal response, GO Cellular Components is associated with extracellular matrix, GO Molecular Functions is related to protein homodimerization activity and receptor ligand activity. KEGG pathways analysis showed that the fibrates were related to HIF-1 signaling pathways in the treatment of IS, among which fenofibrate, pirinixic acid, clofibrate and bezafibrate are strongly correlated with the HIF-1 signaling pathway.

GO functional analysis and KEGG pathway enrichment analysis of fibrates and HIF1A-related genes

GO functional and KEGG pathways of fibrates regulating HIF1A-related genes in the treatment of IS were analyzed (Figs. 9 and 10). GO functional enrichment analysis showed that pilinic acid and clofibrate could better regulate the biological functions of HIF1A-related genes, which could play a role in the prevention and treatment of IS. KEGG pathways analysis showed that there are 21 KEGG pathways belongs to pirinixic acid and HIF1A-related genes, there are 8 KEGG pathways belongs to clofibrate and HIF1A-related genes. KEGG pathway analysis showed that pirinixic acid mainly regulated actin cytoskeleton, oocyte meiosis and focal adhesion pathway of HIF1A-related genes to play a role in the prevention and treatment of IS, clofibrate mainly regulates pathways in cancer, leukocyte transendothelial migration and cAMP signaling pathway of HIF1A-related genes to play a role in the prevention and treatment of IS. The GO functional of fenofibrate and HIF1A-related genes was very few, the KEGG pathway of fenofibrate and HIF1A-related genes was not found, so the GO functional and KEGG pathway of fenofibrate and HIF1A-related genes was not analyzed.

The molecular docking of fibrates and HIF1A

The common gene sets of five fibrates and IS was analyzed, the results showed that only the common gene sets of fenofibrate, pirinixic acid, clofibrate and IS contained the HIF1A. So molecular docking of HIF1A and above three drugs was performed (Fig. 11), the binding energies of the three drugs and HIF1A are shown in Table 2. It has been reported that the affinity between the receptor and ligand can be predicted by binding energies, when

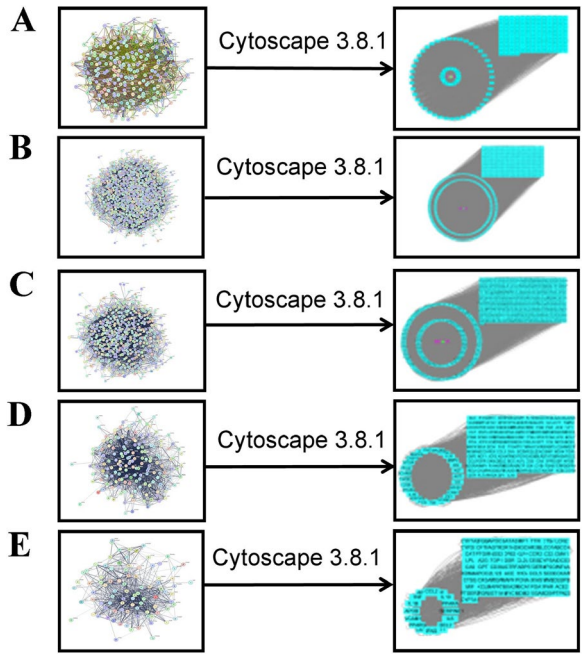

Fig. 5 PPI network diagram of common targets of fibrates and IS: **A** PPI network diagram of common targets of fenofibrate and IS; **B** PPI network diagram of common targets of pirinixic acid and IS; **C** PPI network diagram of common targets of clofibrate and IS; **D** PPI network diagram of common targets of bezafibrate and IS; **E** PPI network diagram of common targets of gemfibrozil and IS

binding energy is less than − 5.0 kcal/mol, it indicates that the combination ability of the receptor and ligand is good [25]. The results of this study show that the binding energy of the above three drugs and HIF1A is less than − 5 kcal/mol, which indicates that these drugs can better bind to HIF1A.

Discussion

Many risk factors can lead to the occurrence of IS, among which hyperlipidemia is a high risk factor [27]. Fibrates are peroxisome proliferator-activated receptor α (PPARα) agonists [28], it can activate the transcription factor PPARα to bind to another transcription factor RXR, which increases the gene transcription and protein expression. Fibrates can play a role in regulating lipid, stable plaque, anti-atherosclerosis and reduce ischemia–reperfusion injury by increasing the activity of various enzymes and participating in oxidative stress response [29]. Therefore, fibrates are often used to prevention and adjuvant treatment IS.

IS is a severe vascular event characterized by local or complete blood flow occlusion in brain tissue, typically caused by plaque obstruction of internal carotid artery or middle cerebral artery [30]. It has the characteristics of high morbidity, high mortality and high disability rate [31–33]. The main factors of leading to brain injury include excitotoxicity of cells, energy metabolism disorders, calcium overload, oxidative stress, cell apoptosis, autophagy and inflammatory response in the pathological process of IS [34]. When the brain is hypoxic/ischemic, the body will produce a large number of reactive oxygen species (ROS), these ROS will disrupt the body's biological balance, which will cause oxidative stress, inflammation and apoptosis, then it can lead to brain injury and cerebral ischemia–reperfusion injury [35]. The concentration of ROS can affect the expression of HIF-1A, when the concentration of ROS is high, a large number of biological factors will be produced, the over-expression of these biological factors may cause the disorder of biological functions, then the body is damaged. Fibrates can enhance the activity of antioxidant enzymes and regulate angiotensin II to induce vascular remodeling, which can increase oxygen supply to the brain, then play a role in inhibiting oxidative stress and inflammatory response, which can reduce ischemia–reperfusion damage to brain, so fibrates not only can participate in the process of lipid metabolism, but also play a role in anti-atherosclerosis and reducing ischemia–reperfusion injury, which can effectively play a role in the prevention and treatment of IS. This study explored the relationship between fibrates and HIF1A in the treatment of IS, the results showed that only the common target of fenofibrate, pirinixic acid, clofibrate and IS contained the HIF1A, and these 3 fibrates can regulate HIF1A to prevent and treat IS.

GO function analysis and KEGG pathway analysis showed that fibrates can regulate HIF1A to prevent and treat IS through inflammatory reactions, hormone reactions, pathways in cancer, lipid and atherosclerosis and HIF-1 signaling pathway. The pathogenesis and prognostic mechanism of IS are complex, it is closely related to inflammatory response. Inflammatory reactions is related to a variety of inflammatory factors such as TGF-β, IL-17A, IL-6, IL-21 and IL-22, these factors can cause inflammatory response, then aggravate brain damage, leading to poor outcome [36, 37]. In the process of IS, interleukin (IL) is an important inflammatory regulator, which plays a key role in the process of nerve repair and brain function recovery. Fibrates may reduce the occurrence of vascular inflammation reactions by inhibiting inflammatory factors, it can reduce the level of HIF1A, which can increase cerebral blood perfusion and reduce the occurrence of cerebral hypoxia and ischemia. When IS occurs, hormone levels will be altered, such as the hypothalamic-pituitary-thyroid axis will respond to the ischemic/hypoxic environment, it will reduce the levels of T3 and FT3 and increase the levels of T4 and TSH. On the contrary, if the levels of T3 and FT3 increase and the levels of T4 and TSH decrease, it means that

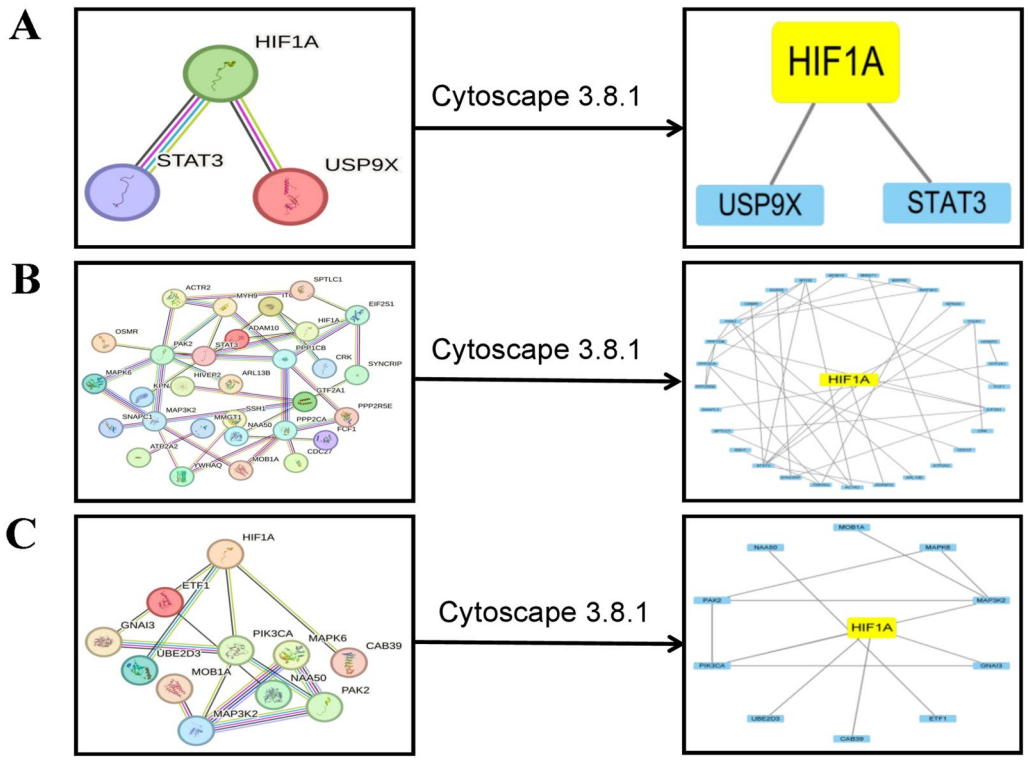

Fig. 6 PPI network diagram of common targets of fibrates and HIF1A-related genes. **A** PPI network diagram of common targets of fenofibrate and HIF1A-related genes; **B** PPI network diagram of common targets of pirinixic acid and HIF1A-related genes; **C** PPI network diagram of common targets of clofibrate and HIF1A-related genes

the patient has already enters the recovery period of IS [38]. KEGG pathway analysis showed that the pathological process of IS is associated with the HIF-1 signaling pathway, HIF-1 is a heterodimeric transcription factor, it consists of HIF-1α and HIF-1β [39], HIF-1α can regulate the expression of some hormones such as erythropoietin and vascular endothelial growth factor [40]. These hormones are related to blood viscosity, the development of collateral vessels and the protection of nerve cells. HIF1A can improve the state of cerebral ischemia and hypoxia by regulating the levels of these hormones, which can reduce the occurrence of IS and promote the recovery of IS. KEGG pathway analysis showed that renal cell carcinoma, thyroid hormone signaling pathway, focal adhesion and pathways in cancer were the main KEGG pathways of fibrates regulate HIF1A-related genes to treat IS, among which the KEGG pathways of pirinixic acid and HIF1A-related genes is the most, which indicated that pirinixic acid may be closely related to HIF1A in the treatment of IS.

At present, the methods of predicting binding energy between small molecules and proteins mainly include AutoDock analysis, MMGBSA/MMPBSA analysis, Discovery Studio analysis, GOLD analysis and MOE-Dock analysis. AutoDock analysis is widely used in molecular docking, which can conveniently and simply calculate the binding energy between small molecules and proteins. MMGBSA/MMPBSA analysis is based on the calculation of static energy, which cannot capture the dynamic process of binding and dissociation. Discovery Studio can calculate the binding energy of molecular docking by geometric matching and energy matching, but it need take a long time. GOLD analysis can calculate the binding energy by genetic algorithm, but it lacks flexibility. MOE-Dock analysis simulates the interaction between two or more molecules by geometric matching and energy matching, then calculates their binding energy, however, MOE-DOCK analysis is expensive. So AutoDock software was used to perform the molecular docking of fibrates and HIF1A gene in this study. Molecular docking results showed that the binding energy of fenofibrate, pirinixic acid, clofibrate and HIF1A is less than − 5 kcal/mol, which indicates that these drugs can better bind to HIF1A. So when dyslipidemia and hypoxia occur, fibrates can activate HIF-1A to regulate blood lipid levels, protect nerve cells and promote the development of collateral vessels, which can reduce the occurrence risk of IS. Finally, the mechanism of the above three drugs

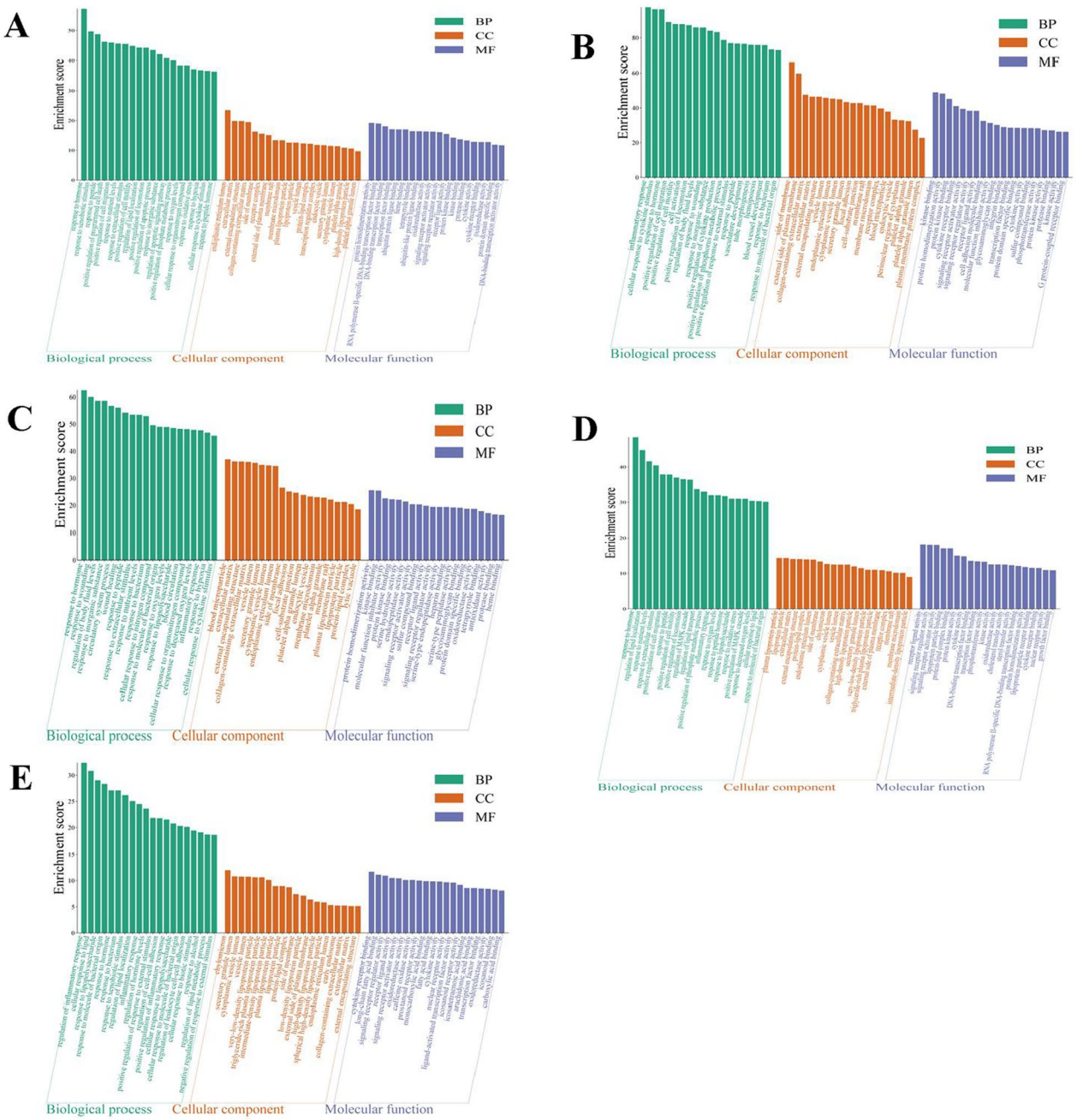

Fig. 7 Enrichement GO term diagram of fibrates in the treatment of IS. **A** Enrichement GO term diagram of fenofibrate in the treatment of IS; **B** enrichement GO term diagram of pirinixic acid in the treatment of IS; **C** enrichement GO term diagram of clofibrate in the treatment of IS; **D** enrichement GO term diagram of bezafibrate in the treatment of IS; **E** enrichement GO term diagram of gemfibrozil in the treatment of IS

regulating HIF1A in the prevention and treatment of IS can be predicted (Fig. 12).

Limitation

The present study has some limitations. Due to time and other limitations, we did not perform animal and cell experiments for validation. Our study initially explored the mechanism by which fibrates regulate HIF1A to treat IS, which is expected to provide some reference for exploring the mechanism of drug regulating gene to treat diseases in the future.

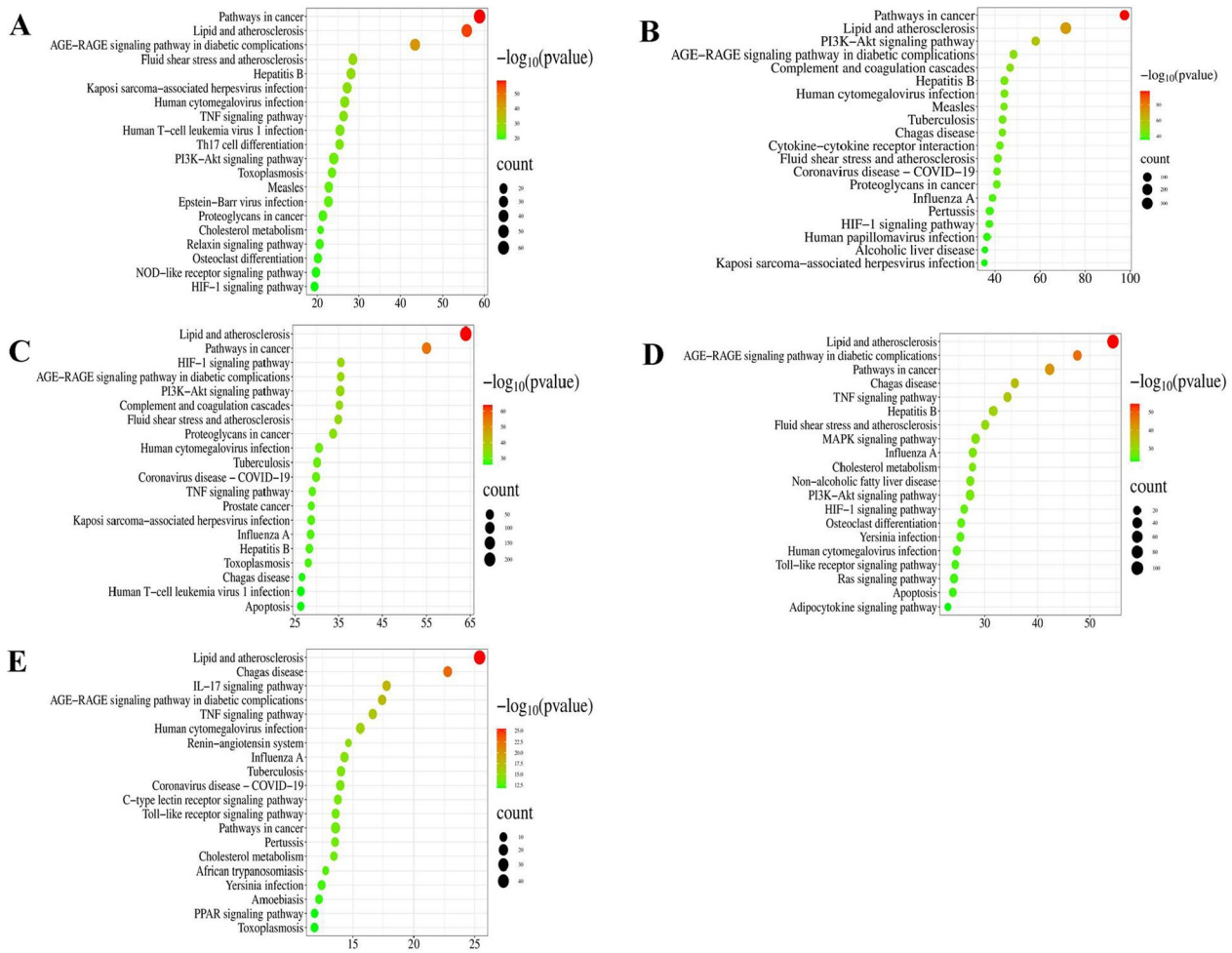

Fig. 8 KEGG pathway bubble diagram of fibrates in the treatment of IS. **A** KEGG pathway bubble diagram of fenofibrate in the treatment of IS; **B** KEGG pathway bubble diagram of pirinixic acid in the treatment of IS; **C** KEGG pathway bubble diagram of clofibrate in the treatment of IS; **D** KEGG pathway bubble diagram of bezafibrate in the treatment of IS; **E** KEGG pathway bubble diagram of gemfibrozil in the treatment of IS

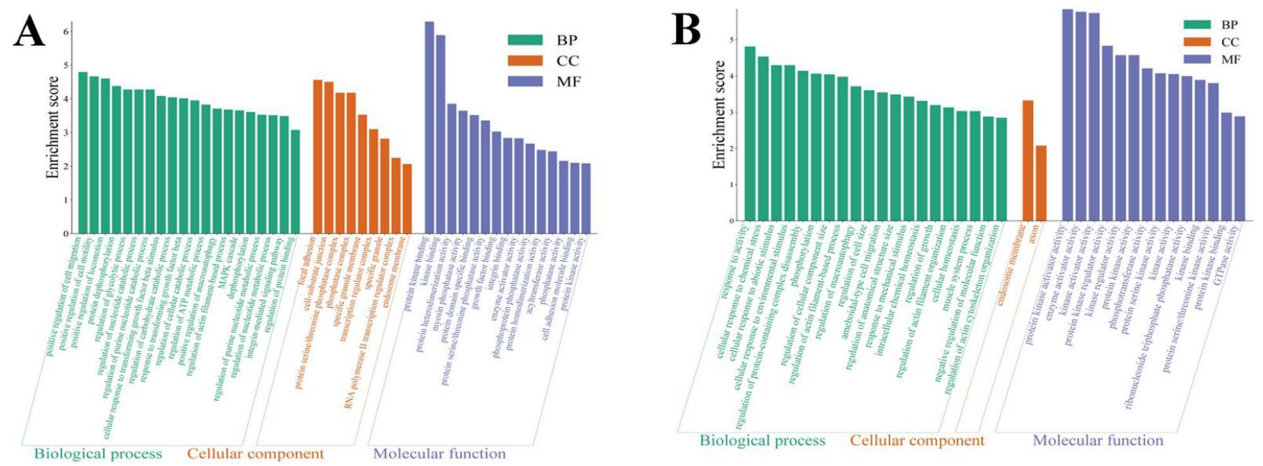

Fig. 9 Enrichement GO term diagram of fibrates regulating HIF1A-related genes in the treatment of IS: **A** enrichement GO term of pirinixic acid regulating HIF1A-related genes in the treatment of IS; **B** enrichement GO term of clofibrate regulating HIF1A-related genes in the treatment of IS

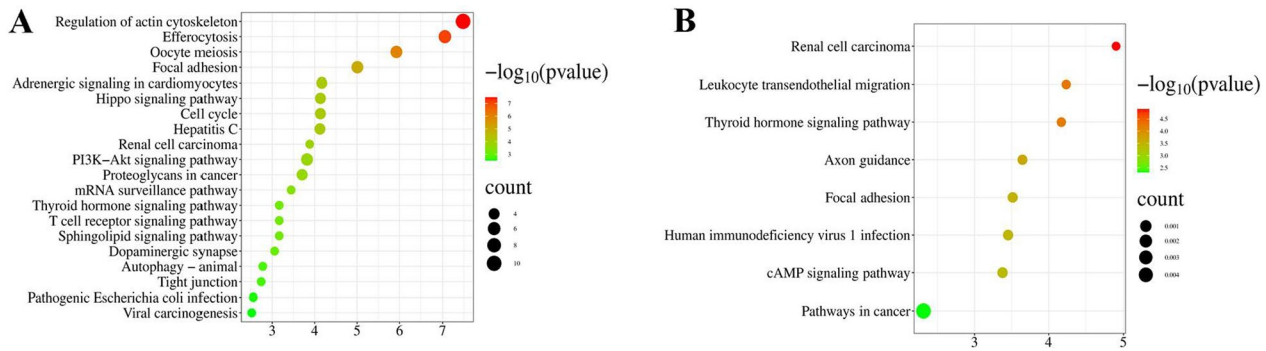

Fig. 10 KEGG pathway bubble diagram of fibrates regulating HIF1A-related genes in the treatment of IS: **A** KEGG pathway bubble diagram of pirinixic acid regulating HIF1A-related genes in the treatment of IS; **B** KEGG pathway bubble diagram of clofibrate regulating HIF1A-related genes in the treatment of IS

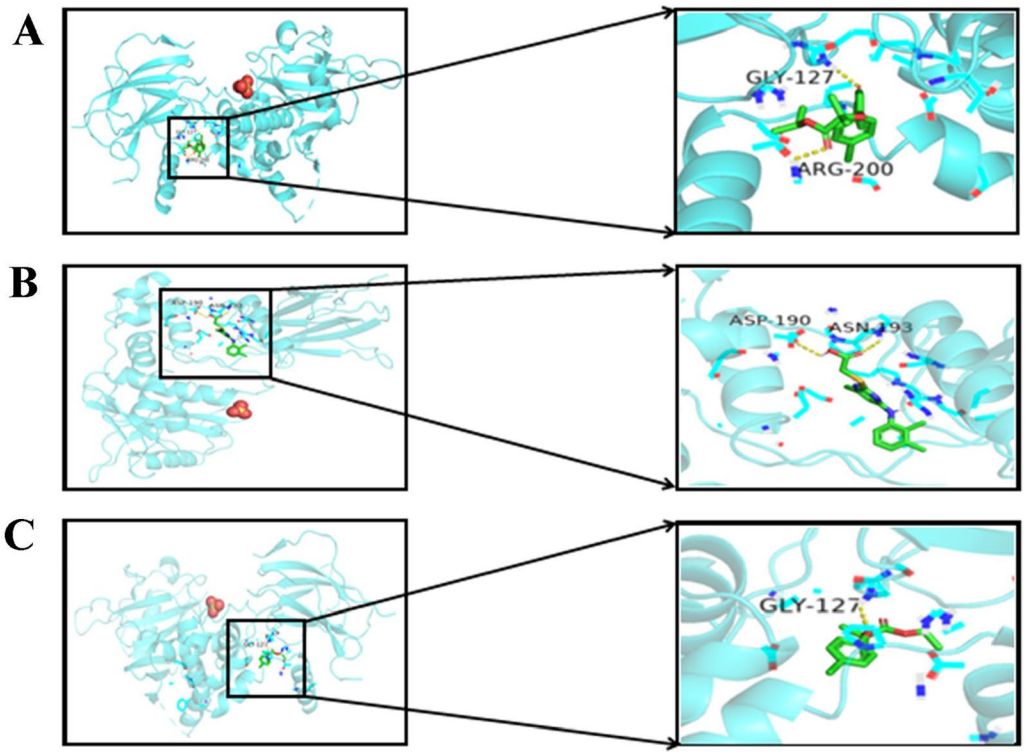

Fig. 11 Molecular docking diagram of fibrates and HIF1A: **A** molecular docking diagram of fenofibrate and HIF1A; **B** molecular docking diagram of pirinixic acid and HIF1A; **C** molecular docking diagram of clofibrate and HIF1A

Table 2 Binding energies of fibrates and HIF1A

Fibrates	Binding energy (kcal/mol)
Fenofibrate	− 7.5
Pirinixic acid	− 7.1
Clofibrate	− 5.6

Conclusion

Fibrates are related to a variety of biological factors in the prevention and treatment of IS, among which fenofibrate, pirinixic acid and clofibrate can regulate HIF1A to participate in the pathological process of IS. Pirinixic acid has a strong correlation with HIF1A

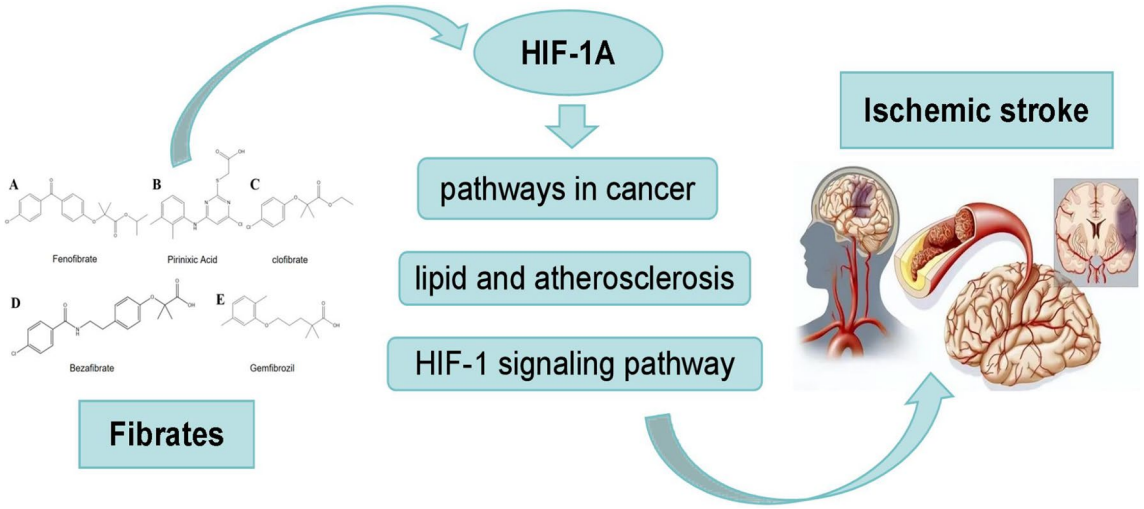

Fig. 12 Graphical abstract

and HIF1A-related genes in the treatment of IS. KEGG pathway analysis showed that the main action pathways of the above 3 fibrates regulating HIF1A in the treatment of IS were pathways in cancer, lipid and atherosclerosis, AGE-RAGE signaling pathway in diabetic complications and HIF-1 signaling pathway. So fibrates can prevent and treat IS through multiple targets, multiple pathways, multiple hormones and multiple biological reactions.

Abbreviations

HIF1A	Hypoxia-inducible factor
IS	Ischemic stroke
PPARα	Peroxisome proliferator-activated receptor α
ROS	Reactive oxygen species
IL	Interleukin

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None.

Author contributions
Conceptualization, P.W.; methodology, Y.Y.; software, F.Y.; validation, X.D.; formal analysis, Z.Y.; resources, J.C.; data curation, M.W.; writing—original draft preparation, F.Y.; writing—review and editing, G.W.; supervision, Y.G.; project administration, G.W. All authors reviewed the manuscript.

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Availability of data and materials
The data of this study can be obtained from the corresponding author [G.W], upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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