The gliptin: one type of potential drug for the treatment of fibrotic diseases

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Abstract

Fibrosis is a common terminal state of many chronic diseases and there are few effective treatments at present. The gliptin is a class of DPP4 inhibitors used in the treatment of type 2 diabetes. At present, many studies show that it may have the effect of inhibiting fibrosis. In order to explore the role of the gliptin in different fibrotic diseases, we searched the related literature about the fibrotic diseases and the gliptin. In our review, we found that the gliptin can inhibit the fibrotic process through a variety of mechanisms. The evidence for the inhibition of atherosclerosis by the gliptin is strong. For pulmonary, renal and cardiac fibrosis, more clinical studies are needed to support it. However, there is no benefit in the treatment of liver fibrosis with the gliptin. To sum up, it is true that the gliptin has the broad-spectrum anti-fibrotic effects.

The gliptin: one type of potential drug for the treatment of fibrotic diseases

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

Abstract

Fibrosis is a common terminal state of many chronic diseases and there are few effective treatments at present. The gliptin is a class of DPP4 inhibitors used in the treatment of type 2 diabetes. At present, many studies show that it may have the effect of inhibiting fibrosis. In order to explore the role of the gliptin in different fibrotic diseases, we searched the related literature about the fibrotic diseases and the gliptin. In our review, we found that the gliptin can inhibit the fibrotic process through a variety of mechanisms. The evidence for the inhibition of atherosclerosis by the gliptin is strong. For pulmonary, renal and cardiac fibrosis, more clinical studies are needed to support it. However, there is no benefit in the treatment of liver fibrosis with the gliptin. To sum up, it is true that the gliptin has the broad-spectrum anti-fibrotic effects.

Key Word

Gliptins **Fibrosis** **DPP4** **Atherosclerosis** **Linagliptin** **Sitagliptin**

Introduction

Fibrotic disease is a general term for the process of chronic diseases caused by improper repair of connective tissue after the tissue damage.Tissue damage can occur in various parts of the body, which also suggests that fibrosis can occur in almost every tissue and organ system.There are two kinds of fibrotic diseases: One is the fibrotic disease confined to specific organs, such as liver fibrosis, kidney fibrosis, myocardial fibrosis, skin fibrosis and so on. The other is the fibrotic disease involving multiple system organs, such as systemic sclerosis, chronic graft vs host disease, etc.

In the pathogenesis of fibrosis, the core element is that fibroblasts are stimulated by various factors to transform into myofibroblasts and secrete excessive extracellular matrix.[1,2] As the T cell surface antigen, DPP4 is a serine protease on the surface of cell membrane which is widely distributed on various cell surfaces including fibroblasts.[3] DPP4 is mainly related to immune regulation, cytokine digestion and T cell activation. Many studies have shown that DPP4 positive fibroblasts are the main effector cells that secrete extracellular matrix and participate in the process of fibrosis, so DPP4 may be a potential target for the treatment of fibrotic diseases.[4-10]

At present, the DPP4 inhibitor that have been used in clinic is the gliptin, which are widely used in the treatment of type Ⅱ diabetes. The gliptin reduces the inactivation of GLP-1 by inhibiting DPP4 activity and increased levels of GLP-1 enhance insulin secretion. The gliptin is a kind of safe, effective and convenient

antihyperglycemic drug because of no weight gain and few hypoglycemic events.

According to the mechanism of action, the existing gliptins can be divided into two categories and their relevant information is described in Table 1. The existing studies have found that the gliptin has an inhibitory effect on a variety of fibrotic diseases.This study aims to summarize and explore the anti-fibrotic effects of the gliptin by searching the literature related to the gliptin used in the fibrosis. (Fig 1)

Pulmonary fibrosis

Pulmonary fibrosis is the end-stage change of many lung diseases, characterized by the proliferation of fibroblasts, the accumulation of extracellular matrix and the destruction of tissue structure.A variety of irritant factors can cause lung inflammation and damage, and further cause pulmonary fibrosis.Idiopathic fibrosis is one of the most important diseases in fibrosis which etiology is unknown and there is no effective treatment at present.

DPP4 is widely distributed on various cell surfaces of the lung, which is considered to be an important antigen deeply involved in lung immune and inflammatory response.[11,12] It has been found that the expression of DPP4 in bronchial epithelial cells increases significantly after lung injury.[13] Inhibition of DPP4 activity can prevent inflammation and vascular injury.[14]

Uncontrolled inflammatory response is also an important cause of initiating pulmonary fibrosis. In the pathogenesis of pulmonary fibrosis, not only the involvement of fibrosis-related TGF-β pathway, but also the epithelial-mesenchymal transition plays an important role.Epithelial-mesenchymal transition is a process in which epithelial cells are transformed into fibroblasts and the abundant epithelial cells in the lung become an important source of fibroblasts in the process of pulmonary fibrosis. [15]

At present, most of the researches on the relationship between the gliptin and pulmonary fibrosis are basic researches. Among them, the studies of vildagliptin and sitagliptin accounts for the highest proportion. Vildagliptin and sitagliptin were found to inhibit pulmonary fibrosis in mice induced by injection of lipopolysaccharide or bleomycin.[15, 17]In the case of alogliptin, it is currently found that it may not have a mitigating effect on pulmonary fibrosis.[21] At present, there are few clinical studies on the relationship between gliptin and pulmonary fibrosis. Vildagliptin and sitagliptin are the most likely potential drugs to treat pulmonary fibrosis.[17]

The different gliptin inhibits pulmonary fibrosis through different mechanisms of action.The effect of sitagliptin is mainly through the regulation of TGF- β signaling pathway.[16, 18, 20] It inhibits pulmonary fibrosis by inhibiting the TGF- β pathway to reduce the inflammatory response and the degree of activity of fibroblasts. Vildagliptin can further reduce extracellular matrix deposition by inhibiting epithelial-to-mesenchymal transition, thus alleviating the process of pulmonary fibrosis. One of the most important findings in these studies is that the antifibrotic effect of gliptin is also found in animal models without diabetes, showing that gliptin has a direct inhibitory effect on fibrosis partly independent of the regulation of diabetes.Of course, given that diabetes may be one of the risk factors for pulmonary fibrosis,[22] the gliptin may suppress pulmonary fibrosis of diabetic rats in part by inhibiting diabetes.

It is worth noting that asthma is also a type of lung disease that can cause pulmonary fibrosis. It has been shown in the literature that saxagliptin and sitagliptin can inhibit asthma by inhibiting the inflammatory response in the airway and the production of related cytokines.[16,19]

In general, the inhibitory effect of gliptin on pulmonary fibrosis is mainly reflected in basic research and more clinical studies are needed to prove it.(Table 2)

Liver fibrosis

Liver fibrosis is a common terminal state of many liver diseases. Many kinds of injury factors lead to liver over-repair and eventually lead to liver fibrosis.[23,24,25] Hepatic stellate cell (HSC) is a unique and

important factor in the development of hepatic fibrosis. Hepatic stellate cell are the mesenchymal cell of the liver, which are in a resting state under the normal condition. In that proces of liver fibrosis, the hepatic stellate cell are activated by various factors to transform into myofibroblasts, which participate in the synthesis of extracellular matrix and structure remodeling , and finally lead to the formation of liver fibrosis.[26,27,28] Nonalcoholic fatty liver disease (NAFLD) is an important cause of liver fibrosis, which affects more than 70% of patients with type-2 diabetes.[29] Currently, there is a lack of drug that can reverse liver fibrosis.

At present, there are many studies on the relationship between the gliptin and liver fibrosis, but the conclusions of basic research and clinical research are obviously different or even contrary.In that basic study, liver fibrosis is induce in mice by carbon tetrachloride, pig serum or streptozotocin, regardless of whether the mice also have diabetes or non-alcoholic liver disease, the gliptins are able to inhibit liver fibrosis in mice.[30,31,33-36,41,43-46,48] The combination of gliptin with pioglitazone [31], oleanolic acid (TGR5 agonist),[32, 43] Emmagliflozin (an SGLT2 inhibitor),[33] Canagliflozin[37] or Silymarin[44] can produce a synergistic effect.

But the results of the clinical studies are far from satisfactory. Current clinical studies have mainly been associated with sitagliptin, but most [40, 41, 47] have shown that sitagliptin does not inhibit liver fibrosis and non-steatoalcoholic hepatitis in patients with or without diabetes.There is even a literature[39] that suggests that gliptins increase the incidence of hepatic decompensation in cirrhotic patients.

The anti-fibrotic effect of the gliptin is mainly through inhibiting hepatic stellate cells, inflammatory reaction, TGF- β pathway and NF-kB pathway. Secondly, some studies have shown that GLP-1 can inhibit liver fibrosis and inflammatory reaction, thus playing a protective role in liver. GLP-1 receptor agonists may be potential drugs to inhibit liver fibrosis.[49,50] Therefore, the inhibition of liver fibrosis by the gliptin may be partly mediated by the effect on GLP-1.

Given the reliability of the clinical evidence, we believe that the gliptin may not be able to inhibit liver fibrosis in patients.(Table 2)

Renal fibrosis

Renal fibrosis is the end stage of many renal diseases, which is mainly manifested by the reduction of intrinsic cells, the deposition of extracellular matrix and the inevitable renal failure.When the kidney is stimulated by a variety of injury factors, a series of inflammatory response factors can transform the intrinsic cells and fibroblasts of the kidney into myofibroblasts which lead to the excessive secretion of collagen and other extracellular matrix. TGF- β pathway and epithelial-mesenchymal transition are the main processes involved in renal fibrosis.

In all organ, the expression level of DPP4 is the highest in the kidney. It is widely expressed on the cell membrane of podocytes, mesangial cells, proximal tubule cells and deeply participate in the process of the tissue structure remodeling and epithelial-mesenchymal transformation of kidney.[70-73] Crescent is an important marker of nephritis formation. It has been found that DPP4 is highly expressed in the crescents in different nephritis models.[52]

Most of the current studies on the role of gliptins in renal fibrosis are basic studies, with the largest number of studies on sitagliptin and linagliptin. Renal fibrosis is induced in mice by injection of streptomycin [57, 61, 62, 64, 67], unilateral ureteral ligation[54, 65, 68] and other methods[54-56, 58-60, 63, 65, 66, 68, 69]. It is then found that the gliptin can inhibit the process of renal fibrosis or renal interstitial fibrosis and this inhibition is greater than that of telmisartan[59, 61].

The inhibitory effect of gliptin on the progression of renal fibrosis is mainly through the inhibition of inflammatory injury, TGF- β pathway and epithelial-mesenchymal transition. Diabetes is one of the

important factors causing renal injury and is closely related to the occurrence of renal fibrosis[74]. By inhibiting the progression of diabetes, the gliptin inevitably slow the progression of renal fibrosis partly dependent on the regulation of GLP-1[66]. However, the inhibitory effect of the gliptin on renal fibrosis can be independent of the regulation of blood glucose[54, 55, 56, 58, 59, 60, 66, 69]. Linagliptin inhibits the formation of the crescent and inhibits the process of renal fibrosis by modulating the immune response[52].

On the whole, sitagliptin and linagliptin may be effective enough to inhibit renal fibrosis, but more clinical studies are needed to prove it.(Table 2)

Cardiac fibrosis

Insufficient blood supply of coronary artery leads to repeated ischemia and anoxia of myocardial cells, which will eventually lead to myocardial fibrosis. Myocardial fibrosis can lead to decreased cardiac compliance, which in turn causes ventricular diastolic and systolic dysfunction, and even arrhythmia.

Normally, fibroblasts located in the interstitial and perivascular spaces secrete a small amount of collagen for maintaining the basic mechanical strength and cytoskeleton of the cardiovascular tissue. Myocardial fibrosis occurs when collagen accumulation is caused by excessive secretion or decreased degradation of collagen.

The unique and important pathogenesis of cardiac fibrosis is the mechanism of angiotensin Ⅱ. Angiotensin Ⅱ increases and combines with its receptor, which promotes the transformation of myofibroblasts and the activation of TGF-β1 pathway and finally accelerates cardiac fibrosis[75, 99, 100].

GLP-1 receptors are widely distributed in the cardiovascular system including cardiomyocytes and endothelial cells and GLP-1 is thought to have protective effects on heart injury, which is mainly mediated by mechanisms such as PIK3, AKT and p38[101-104]. The protective effect of GLP - 1 on the heart naturally has some inhibitory effect on myocardial fibrosis.

At present, most of the studies on the relationship between the gliptin and cardiac fibrosis are basic studies. Studies have shown that linagliptin[77-82], sitagliptin[91-98], saxagliptin[83-85] and vildagliptin[86-90] can inhibit cardiac fibrosis. The inhibitory effect of gliptin on myocardial fibrosis seems to be partly independent of blood glucose regulation. The inhibitory effect of vildagliptin on cardiac fibrosis is similar to that of enalapril [88, 89].

Firstly, the inhibition of cardiac fibrosis by gliptin acts by inhibiting the initial factors. Gliptin can inhibit the production of reactive oxygen species[76, 77, 81, 92, 95] and inflammatory factors[78, 92], thereby reducing the stress damage caused by ischemia and hypoxia and finally slowing down the occurrence of cardiac fibrosis. Secondly, the effect of angiotensin Ⅱ on the acceleration of cardiac fibrosis is inhibited by the gliptin[80, 82, 85]. Finally, the gliptin can increase the level of GLP-1 and exert the cardioprotective effect through the downstream pathways of AKT, PIK3 and p38, and finally inhibit the fibrosis of the heart[82, 87, 88, 91, 96, 97].(Table 2)

Atherosclerosis

The main characteristics of vascular fibrosis are excessive deposition of extracellular matrix, hardening of vascular wall and thickening of vascular wall. Vascular fibrosis can cause a range of clinical diseases, the most important of which is atherosclerosis[124 - 126]. Under the action of a variety of stimulating factors, smooth muscle cells, macrophages, T cells and endothelial cells participate in the process of arteriosclerosis, resulting in excessive collagen and relatively lack of elastin in the vascular wall[127-129].

The main pathological mechanisms involved in atherosclerosis are abnormal activation of the TGF-β pathway, activation of the RAAS system and increased levels of oxidative damage, which ultimately contribute to the development of vascular fibrous hyperplasia[130].

At present, there are many basic and clinical studies on atherosclerosis and the gliptin.

Basic studies have shown that the gliptin can inhibit atherosclerosis in diabetic mice[105, 106, 108, 111, 120] and non-diabetic mice[109, 113, 114, 116, 117]. Clinical studies have shown that the gliptin can prevent the occurrence of atherosclerosis in patients with diabetes[107, 115, 118, 119, 121-123], which is rarely reported in non-diabetic patients. In the prevention of atherosclerosis, the combination of gliptin and insulin or metformin has a synergistic effect[118, 121, 123]. For patients who have already developed atherosclerotic plaques, the gliptin may not have the effect of reducing the plaque[122].

This inhibition is mediated mainly by two important pathways. The first is the GLP - 1 pathway, in which a statin can up-regulate GLP - 1 in the blood. On the one hand, GLP-1 has a direct protective effect on blood vessels and can directly inhibit inflammation of blood vessels[131]. On the other hand, GLP-1 can slow down the progression of diabetes, thus indirectly slowing down the vascular damage caused by diabetes[132].

Next is the inhibitory effect of the gliptin by promoting the polarization of macrophage. Macrophage is an important subpopulation of cell involved in a variety of inflammatory responses[133]. First of all, one of the most important initiation factors in the development of atherosclerosis is the occurrence of inflammatory damage. Macrophage is divided into M1 and M2[134], the former promotes inflammatory reaction, the latter inhibits inflammatory reaction. Up-regulation of the proportion of M1-type macrophages can promote the occurrence of vascular fibrosis and up-regulation of the proportion of M2 type macrophages could inhibit the occurrence of atherosclerosis[135, 136]. Secondly, macrophage is involved in the formation of foam cells, an important event in the early stages of atherosclerosis. DPP4 is an important molecule involved in the immune response and DPP4 inhibitors are found to up-regulate the proportion of M2-type macrophages in the liver and abdominal cavity of mice[137].The studies we collected suggest that the gliptin can inhibit the development of atherosclerosis by increasing the proportion of M2-type macrophages and inhibiting macrophage-related functions[109, 124, 127, 120].

On the whole, sitagliptin may be the best drug to inhibit atherosclerosis among the gliptins.(Table 2)

Other fibrosis

In addition to the common fibrotic diseases, there is currently a small amount of researches on the use of the gliptin for other fibrotic diseases.

Basic studies have shown that the gliptin inhibits catheter-related peritoneal fibrosis after dialysis138, ovarian fibrosis[139], fatty fibrosis[144], hypertrophic scars[143] and systemic sclerosis[142]. Some clinical studies have shown that the gliptin can also reduce the occurrence of cystic fibrosis[140], keloids[146] and chronic graft vs host disease[145]. The major pathophysiological processes of chronic graft vs host disease also involve vascular fibrosis.

The inhibitory effect of the gliptin on these fibrotic diseases is mainly through inhibiting the immune function of DPP4 and TGF-β pathway. The risk of hypoglycaemia associated with the use of gliptin is low. Therefore, the gliptin may be effective in the treatment of these fibrotic diseases alone or in combination [147-149] with other drugs. Although there are few studies at present, it provides some enlightenment for the further clinical study on the application of gliptin in the treatment of fibrotic diseases.(Table 2)

The most promising drug candidates

Based on our statistical results, we found that sitagliptin and linagliptin are the most promising gliptins in terms of anti-fibrosis.

There is a lack of literature on licagliptin in pulmonary fibrosis, but it has been shown to be effective in inhibiting other types of fibrosis except liver fibrosis. In addition, linagliptin has the unique anti-fibrotic mechanism and advantage. DPP4, as a kind of important cell surface marker, can promote the activation of TGF-β pathway and its downstream epithelial-stromal transformation by binding with integrin β , thus

accelerating the development of fibrosis[24]. Linagliptin can inhibit the activation of TGF- β pathway by inhibiting the integrin β pathway, which is the unique mechanism of linagliptin[65]. Moreover, linagliptin is the only type of gliptin that does not need to be adjusted according to the liver and kidney function of the patient. Therefore, we consider it an important candidate for anti-fibrosis drug.

Sitagliptin is also an important drug candidate. Not only does sitagliptin account for the largest proportion of the literature, but sitagliptin can inhibit all types of fibrosis except liver fibrosis. Moreover, more than 80% of the clinical research literature is about sitagliptin, indicating that it has the greatest anti-fibrotic potential.(Fig 2)

Conclusion

In general, that evidence for the inhibition of a variety of fibrotic disease, especially in the inhibition of atherosclerosis, is strong. In lung, kidney and heart fibrosis, more clinical studies are needed to prove it. It is important to note that the gliptin may have no significant effect on inhibiting liver fibrosis.

The inhibition of fibrotic disease by statin drugs works through a variety of mechanisms, such as TGF-β, ECM, antioxidant damage, GLP-1 and so on. The anti-fibrotic drugs currently in development work mainly through seven mechanisms[150] and five of them are related to the mechanism of action of the gliptin. Not only that, the antifibrotic range of the gliptin encompasses almost all of the drugs currently in the R & D phase.[150] These suggest that the role of the gliptin in the field of anti-fibrotic therapy cannot be underestimated.(Fig 3)

Basic researches suggest that the inhibitory effect of the gliptin on the fibrotic diseases can be independent of diabetes. Our study identified sitagliptin and linagliptin were the most promising anti-fibrotic drugs. However, most of the clinical studies on the relationship between the gliptin and fibrotic diseases involve patients with diabetes mellitus, which leads to the need for more clinical evidences or trials to show that the gliptin also has an inhibitory effect on fibrotic disease in non-diabetic patients.

Table 1 Classification of the gliptins

	Peptide Mimetic	Non-Peptide Mimetic
Representative Drugs	Sitagliptin,Saxagliptin,Vildagliptin	Alogliptin,Linagliptin
the Mechanism of Action	Mimic the DPP4 enzyme substrate structure and bind to the DPP4 site competitively.	Specifically binding to the DPP4 active site, thereby inactivating DPP4.
Characteristics of Function	Low selectivity, non-covalent binding and low specificity.	High selectivity, high specificity, and thus long-lasting drug effect without multiple administration

Table 2 Literatures on the study of gliptins in fibrotic diseases

Pulmonary Fibrosis						
	Object	**Result**	**Mechanism**	**Size***	**Drug**	**Diabetic or HG-treatment**
Manar G. Helal,2019[19]	Rats with acute allergic asthma	Marked antiasthmatic effect	NF-κB	10	Sa	N
Toshio Suzuki,2017[15]	Rats with lung	Ameliorate pulmonary fibrosis	EMT，DPP4	5	Vi	N

	injury					
Yang Liu,2020[17]	Rats with idiopathic pulmonary fibrosis	A promising therapeutic candidate for idiopathic pulmonary fibrosis.	DPP4,ECM	9	Vi	N
Xiuwu Liu,2020[18]	TGF β -activated human lung fibroblasts	Inhibits fibroblasts	TGF- β	⩾3	Si	N
Manar A. Nader,2015[16]	Mice with chronic asthma	Relieve asthma	Inflammation,TGF- β ,ROS	10	Si	N
Jian Xu,2018[20]	Rats with pulmonary hypertension	Inhibit pulmonary arterial adventitia fibrosis	EMT,inflammation	8	Si	N
Shota Hodono,2018[21]	Rats with pulmonary fibrosis	Don't ameliorate pulmonary fibrosis after lung injury	----------	7	Al	N
Liver Fibrosis						
Hanyan Zhang,2019[30]	Rats with CCl_4-induced liver fibrosis	Alleviate liver fibrosis	Stellate cell	7	Al	N
Yuichiro Amano,2018[31]	Rats with modified choline-deficient L-amino acid-defined diet	Combination therapy (pioglitazone+Al) can inhibit nonalcoholic fatty liver disease and its fibrotic process	----------	16	Al	Y
Daisuke Kaya,2019[32]	Diabetic rats with liver fibrosis	Inhibit liver fibrosis. A synergistic effect when used in combination with oleanolic acid(TGR5 agonist)	Stellate cell	10	An	Y
Teruo Jojima,2016[33]	Diabetic rats with non-alcoholic steatohepatitis	Inhibit liver fibrosis. A synergistic effect when used in combination with Empagliflozin (an SGLT2 inhibitor)	----------	6	Li	Y
Thomas Klein,2014[34]	Rats with non-alcoholic steatohepatitis	Inhibit liver fibrosis.	DPP4,macrophage,inflammation	7	Li	N
Yara M. Aboulmagd,2020[35]	Obesity rats with diabetes	Inhibit liver fibrosis.	Inflammation,ECM	6	Li	Y
Xiaoyu Wang,2016[36]	Rats with non-alcoholic steatohepatitis	Mild direct anti-fibrotic properties	ROS,macrophage,inflammation	7	Si，Li	N
Takahiro Ozutsum,2020[37]	Rats with liver fibrosis	Inhibit liver fibrosis. A synergistic effect when used in combination with Canagliflozin	TGF- β ,ECM	10	Te	N
Rania Khalil,2020[38]	Rats with CCl_4-induced liver fibrosis	A hopeful candidate for adjuvant treatment of liver fibrosis.	ERK1/2, p38 α ,NF- κ B	15	Vi	N

Fu- Shun Yen,2021[39]	Diabetic patients with liver cirrhosis	Accelerate cirrhosis Decompensation.	----------	2828	Gliptins	Y
Jeffrey Cui,2016[40]	Prediabetic patients with nonalcoholic fatty liver disease	Safe but not better than placebo in reducing liver fibrosis in patients.	----------	50	Si	Y
Kosuke Kaji,2012[41]	Pigs with serum-induced liver fibrosis	May represent a potential new therapeutic strategy against liver fibrosis	ERK1/2, p38,TGF-β, stellate cell,ECM	10	Si	N
Mark M. Smits,2016[42]	Patients with hepatic steatosis and fibrosis	Do not reduce hepatic steatosis or fibrosis in type 2 diabetes patients.	-------	52	Si	Y
Naotaka Shimozato,2019[43]	Nonalcoholic fatty liver disease in rats with liver fibrosis	Combination therapy (OCA+Si)imay be more beneficial for reducing atherosclerosis	stellate cell	50	Si	N
Samia Salem Sokar,2017[44]	Rats with CCl_4-induced liver fibrosis	Inhibit liver fibrosis. A synergistic effect when used in combination with Silymarin	TGF-β,ROS,inflammation	8	Si	N
Shahinul Alam,2018[45]	Patients with nonalcoholic fatty liver disease	Ameliorates steatosis and ballooning, irrespective of diabetes.	---------	40	Si	N
TAKUMI ONOYAMA,2015[46]	Rats with non-alcoholic steatohepatitis	Attenuate hepatic fibrosis	Inflammation,ROS,stellate cell	10	Si	Y
Tisha R Joy,2017[47]	Patients with non-alcoholic steatohepatitis	Does not improve fibrosis score or NAS after 24 weeks of therapy.	---------	6	Si	N
Yun-A. Jung,2014[48]	Rats with steatohepatitis	Decreased liver fibrosis.	---------	5	Si	N
Kidney Fibrosis						
Takahiro Uchida,2017[54]	Rats with acute renal injury	Alleviate renal fibrosis	Macrophage,inflammation,TGF-β.	9	Al	N
Jung Beom Seo,2018[55]	Rats with acute renal injury	Alleviate renal fibrosis	Inflammation(NLRP3), TGF-β	6	Ge	N
Anna-Lena Mayer,2016[56]	Rats with nephritis	Alleviate renal fibrosis	Macrophage,inflammation	11	Li	N
Keizo Kanasaki,2014[57]	Diabetic-2 rats with renal fibrosis	Alleviate renal fibrosis	EMT	6	Li	Y
Muralikrishna,2015[58]	Rats	Inhibition expression of fibronectin	TGF-β	9	Li	N
Oleg Tsuprykov,2016[59]	Rats with chronic renal disease	Ameliorate interstitial fibrosis(no less than that of telmisartan). No	————————	14	Li	N

		obvious effect on perivascular fibrosis of kidney				
Masako Uchii,2016[60]	Hypertensive rats	Reduce renal fibrosis caused by renal injury	Inflammation,DPP4	10	Sa	N
Muralikrishna,2016[61]	Diabetic-1 rats	Alleviate renal fibrosis(better than telmisartan)	TGF-β	8	Sa	Y
Wei Jing Liu,2011[62]	Diabetic-2 rats	Delay glomerular and tubulointerstitial fibrosis	TGF-β,DPP4	8	Vi	Y
Cristina Mega,2011[63]	Diabetic-2 rats	Ameliorate interstitial fibrosis,long-term use of lower doses is better	————————	8	Si	Y
Dongdong Wang,2018[64]	Diabetic-2 rats	Inhibit progressive renal fibrosis.	TGF-β,ECM	8	Si	Y
Esther Civantos,2017[65]	Diabetic-2 rats	Ameliorate interstitial fibrosis	ROS	6	Si	Y
Jian Xu,2018[66]	Kidney-damaged rats	Alleviate renal fibrosis(same as liraglutide(GLP-1R agonist))	GLP-1	8	Si	N
LUXIN LI,2019[67]	Diabetic-1 rats	Significantly inhibit renal fibrosis.	TGF-β	7	Si	Y
Md. Ashraful Alam,2015[68]	Diabetic nephropathy and renal hypertension rats	Prevent renal fibrosis	ROS	6	Si	Y
Chor Ho Jo,2018[69]	Rats with hypertension and renal injury	Ameliorate interstitial fibrosis	Inflammation(NLRP3)	5,5	Si,Li	N
Cardiac Fibrosis						
Xiaowei Zhang,2018[76]	Rabbits	Alleviate interstitial fibrosis	ROS	10	Al	N
Annayya R. Aroor,2013[77]	Obesity rats	Alleviate cardiac fibrosis	ROS	11	Li	N
Annayya R. Aroor,2017[78]	Obesity rats	Inhibit the production of collagen and cardiac fibrosis	Inflammation	10	Li	N
Hiroyuki Hirakawa,2015[79]	Autoimmune myocarditis rats	Remarkably suppressed cardiac fibrosis	Inflammation	19	Li	N
Li-Hui Zhang,2015[80]	AngII-infused rats	Inhibit cardiac fibrosis	Ang Ⅱ	6	Li	N
Tazuru Igarashi,2018[81]	Atrial fibrillation dogs	Inhibit the myocardial fibrosis	ROS	8	Li	N
Xian-wei WANG,2016[82]	Mouse cardiac fibroblasts	Inhibit collagen formation	ERK/NF-κB pathway.	5	Li	Y
Jessica A. Hiemstra,2016[83]	Heart failure rats	Inhibit collagen formation	-------	8	Sa	N
Junichi Ikeda,2016[84]	Myocardial fibrosis mouse	Suppress myocardial fibrosis	DPP4	15	Sa	N
Scott M. Brown,2017[85]	AngII-infused rats	Attenuat periarterial fibrosis	Ang Ⅱ	6	Sa	N
Ahmed A.M,2019[86]	Diabetic-2 rats	May not have a positive impact on fibrotic changes.	-------	16	Vi	Y
Ayako Takahashi,2013[87]	Heart failure rats	Palliate cardiac fibrosis	GLP-1	10	Vi	N
Nattayaporn Apaijai,2016[88]	Diabetic-2 rats	Inhibit cardiac fibrosis (better than enalapril)	ERK1/2	6	Vi	Y

Tharnwimol Inthachai,2015[89]	Rats with cardiac infarction	Inhibit cardiac fibrosis (same as enalapril)	----------	6	Vi	N
Toru Miyoshi,2014[90]	Isoproterenol-treated rats	Attenuat the hypertrophy and perivascular fibrosis	----------	20	Vi	N
Belén Picatoste,2013[91]	Diabetic-2 rats	Alleviate cardiac fibrosis	GLP-1	10	Si	Y
Grazia Esposito,2016[92]	Hypertension rats	Alleviate cardiac fibrosis	NOS, ROS	35	Si	N
Kim Alexander Connelly,2012[93]	Diabetic-1 rats	Inhibit collagen formation	————	6	Si	Y
M. Lenski,2011[94]	Diabetic-2 rats	Prevented myocardial fibrosis	TGF-β	7	Si	Y
Md. Ashraful Alam,2015[95]	Diabetic nephropathy and hypertension rats	Prevented cardiac fibrosis	ROS	6	Si	Y
Nouf M Al-Rasheed,2016[96]	Diabetic-2 rats	Attenuates cardiomyopathy and fibrosis	JAK/STAT	8	Si	Y
Nouf T. Al-Damry,2018[97]	Diabetic-2 rats with cardiomyopathy	Alleviate cardiac fibrosis	LKB-1/AMPK/Akt, apoptosis	8	Si	Y
Yu-Sheng Liu,2015[98]	Diabetic-2 rats	Alleviate cardiac fibrosis	----------	20	Si	Y
Atherosclerosis						
Michishige Terasaki,2017[105]	ApoE−/− rats(diabetic)	Combination therapy (SGLT2i+Al)imay be more beneficial for reducing atherosclerosis	----------	8	Al	Y
Nga N. Ta, MS,2011[106]	ApoE−/− rats(diabetic)	Inhibit atherosclerosis	Monocyte,Inflammation	8	Al	Y
Tomoya Mita,2016[107]	Patients with atherosclerosis	Inhibit atherosclerosis	---------	172	Al	Y
Zubair Shah,2011[108]	LDLR-/- rats fed with a high fat diet	Inhibit atherosclerosis	Monocyte	15	Al	Y
Tsutomu Hirano,2016[109]	Cholesterol-fed rabbit	Can substantially suppress plaque formation in coronary arteries	Inflammation,Macrophage	16	An	N
Hwan-Jin Hwang,2015[110]	Human umbilical vein endothelial cells and THP-1 cells.	Inhibit atherosclerosis	NF-κB , JNK,	3	Ge	N
Camila Manrique,2016[111]	Rats with vascular abnormalities	Inhibit atherosclerosis	--------	10	Li	Y
Haoran Wang,2020[112]	Oxidized LDL-Induced THP-1 Macrophage Foam Cell	Prevent foam cell formation in vitro	---------	5	Li	N
Hotimah Masdan Salim, 2016[113]	ApoE−/− rats(no diabetic)	Inhibit atherosclerosis	ROS,DPP4, Endothelial cells	16	Li	N
Shuhei Nishida,2020[114]	High fat diet	Inhibit atherosclerosis	DPP4,Macrophage	21	Li	Y

	(HFD)-fed Apoe/ mice					
Stefanie A. de Boer,2017[115]	Early diabetes patients with atherosclerosis	Inhibit arterial stiffness.	----------	22	Li	Y
Kunduziayi Aini,2019[116]	ApoE−/− rats(no diabetic)	Inhibit atherosclerosis	GLP-1	11	Vi	N
Michishige Terasaki,2012[117]	ApoE−/− rats(no diabetic)	Significantly suppressed total aortic atherosclerotic lesions	Macrophage	21	Vi	N
Rehab Werida,2020[118]	Patients with type Ⅱ diabetes mellitus	Combination therapy (DMBG+Vi)imay be more beneficial for reducing atherosclerosis	----------	40	Vi	Y
Bo Li,2020[119]	Diabetic patients with coronary artery sclerosis	Inhibit atherosclerosis significantly.	---------	74	Si	Y
F.Vittone,2012[120]	ApoE−/− rats(diabetic)	Stabilise arteriosclerotic lesions	GLP-1,Monocyte,Macrophage,MMP	10	Si	Y
Tomoya Mita,2017[121]	Patients with type Ⅱ diabetes	Combination therapy (insulin+Si)imay be more beneficial for reducing atherosclerosis	----------	137	Si	Y
Tsuyoshi Nozue,2016[122]	Diabetes patients undergone coronary intervention	Do not significantly reduce coronary plaque volume.	----------	28	Si	Y
Xiaojie Liu,2017[123]	Patients with type Ⅱ diabetes	Combination therapy (DMBG+Si)imay be more beneficial for reducing atherosclerosis	----------	44	Si	Y
Other Fibrosis						
Takuo Nagai,2016[138]	Rats with peritoneal fibrosis	Ameliorate peritoneal fibrosis.	TGF-β,GLP-1	6	Li	N
Fang Wang,2019[139]	Rats with ovarian fibrosis	Delays the process of ovarian fibrosis	TGF-β	10	Si	Y
SamuelT.Olatunbosun,2021[140]	Patients with cystic fibrosis	Delay the progress of cystic fibrosis	Be related to diabetes control, not a direct effect	3	Si	Y
Yi-Chen Li,2021[141]	Patients with Peritoneal dialysis	Reduce the incidence of fibrosis after peritoneal dialysis	EMT	19828	Si	Y
Alina Soare,2020[142]	Dermal fibroblasts from human systemic sclerosis	Inhibit fibroblasts	TGF-β	6	Si，Vi	N

Yan Li,2019[143]	Fibroblasts derived from hypertrophic scar	inhibits high glucose-induced transdifferentiation of hypertrophic scar-derived fibroblasts to myofibroblasts	IGF/Akt/mTOR	6	Li	Y
Ana Patrícia,2018[144]	Obese rats	Prevents fibrosis formation in adipose tissue.	----------	10	Vi	Y
Sherif S. Farag,2021[145]	Patients undergone allogeneic hematopoietic stem cell transplantation	Combination therapy (tacrolimus/sirolimus+Si) resulted in a low incidence of grade II to IV acute GVHD	DPP4	36	Si	N
Hirotsugu Suwanai,2020[146]	Sternotomy patients	Suppress the onset of hypertrophic scars or keloids after surgery in humans	----------	5430	Gliptins	Y

Li:Linagliptin; An: Anagliptin; Te:Teneligliptin;Sa:Saxagliptin; Vi:Vildagliptin; Si:Sitagliptin; Al:Alogliptin; Ge:Gemigliptin;Y:Yes; N:No; HG: High glucose ; NAS:NAFLD Activity Score; ROS:reactive oxygen species;Size*:Sample size of experimental group;ApoE:apolipoprotein E gene; LDLR: Low-Density Lipoprotein Receptor

The red portion represents the study which is the clinical literature or in which result doesn't suggest gliptins can inhibit the fibrosis.

Figure 1: the Roadmap of the research

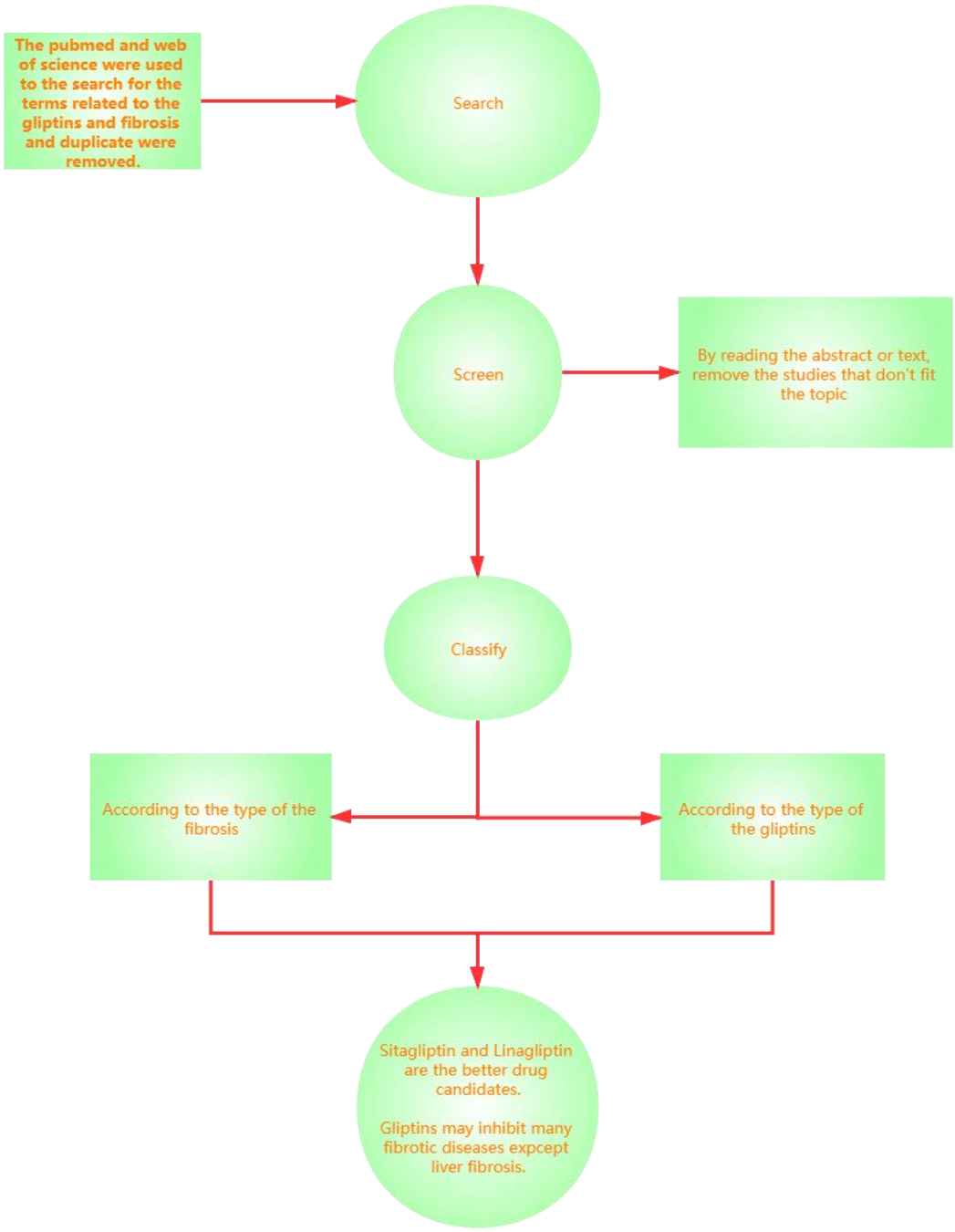


Figure 2: Statistical diagram of the distribution of the researches

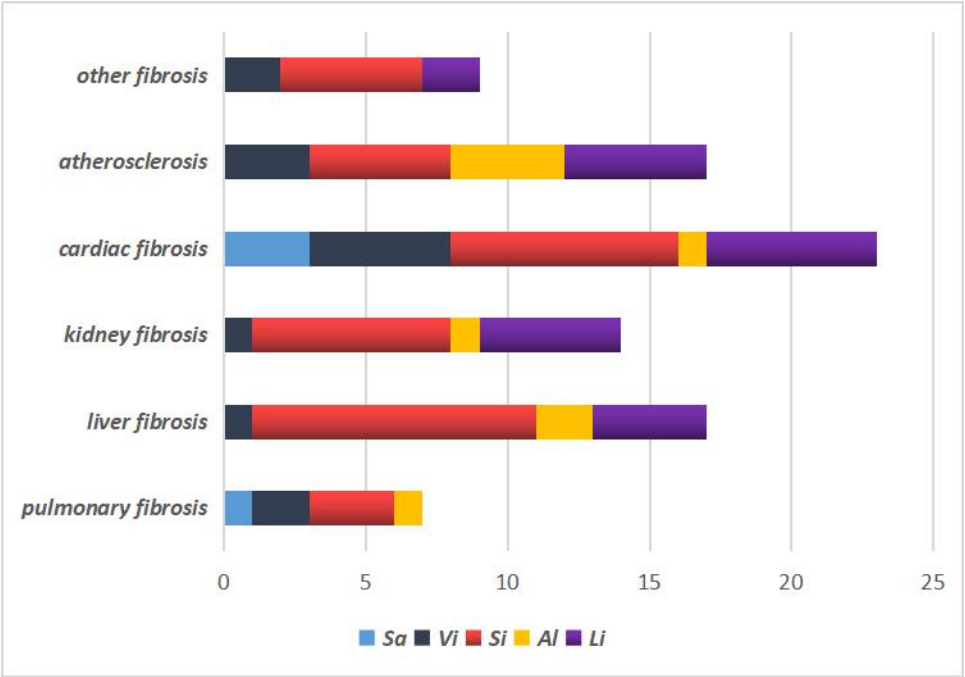
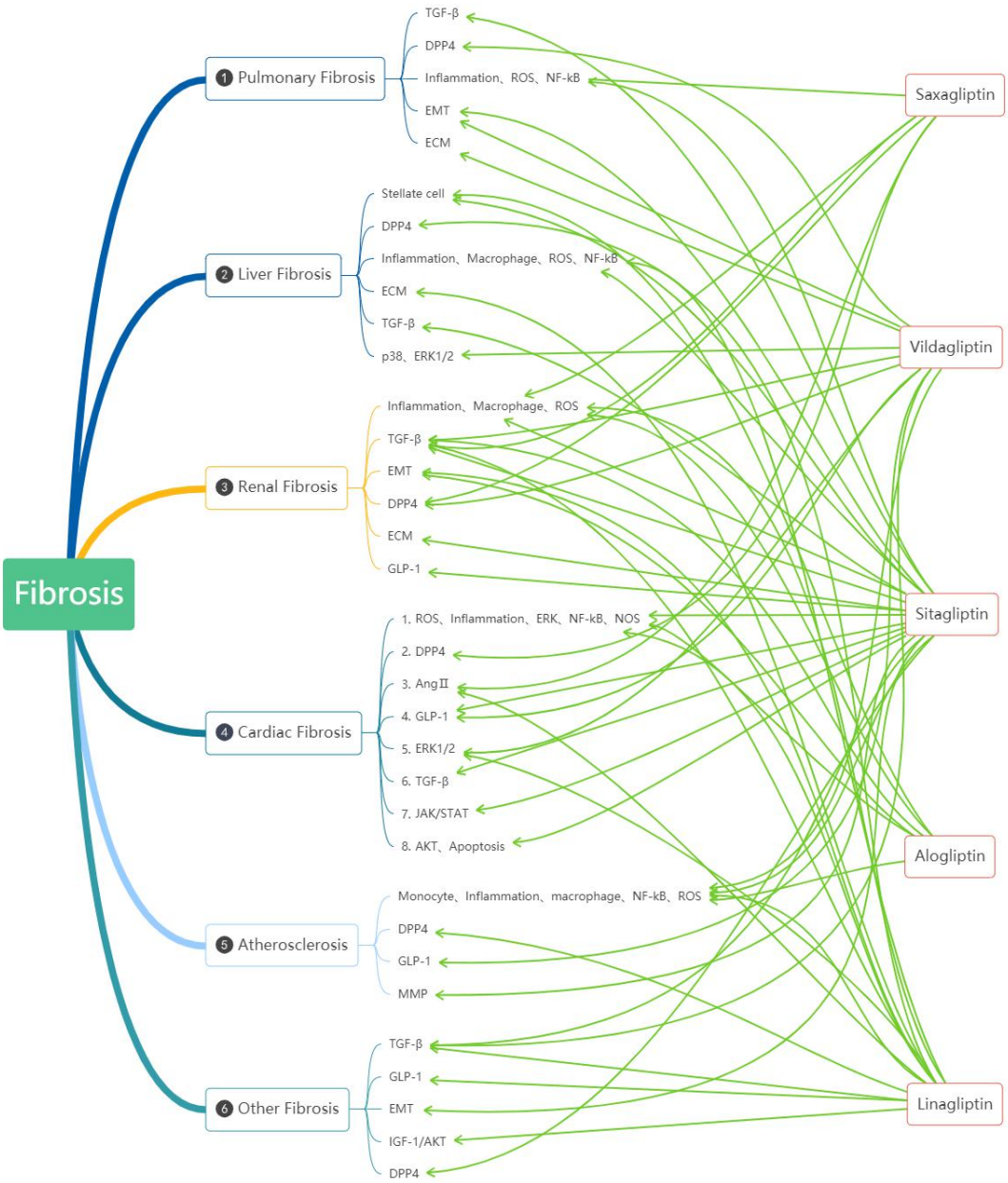


Figure 3: Statistical diagram of anti-fibrotic mechanisms of gliptins



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