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The role of PI3k/AKT signaling pathway in attenuating liver fibrosis: a comprehensive review

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Excessive accumulation of extracellular matrix (ECM) components within the liver leads to a pathological condition known as liver fibrosis. Alcohol abuse, non-alcoholic fatty liver disease (NAFLD), autoimmune issues, and viral hepatitis cause chronic liver injury. Exploring potential therapeutic targets and understanding the molecular mechanisms involved in liver fibrosis are essential for the development of effective interventions. The goal of this comprehensive review is to explain how the PI3K/AKT signaling pathway contributes to the reduction of liver fibrosis. The potential of this pathway as a therapeutic target is investigated through a summary of results from *in vivo* and *in vitro* studies. Studies focusing on PI3K/AKT activation have shown a significant decrease in fibrosis markers and a significant improvement in liver function. The review emphasizes how this pathway may prevent ECM synthesis and hepatic stellate cell (HSC) activation, ultimately reducing the fibrotic response. The specific mechanisms and downstream effectors of the PI3K/AKT pathway in liver fibrosis constitute a rapidly developing field of study. In conclusion, the PI3K/AKT signaling pathway plays a significant role in attenuating liver fibrosis. Its complex role in regulating HSC activation and ECM production, demonstrated both *in vitro* and *in vivo*, underscores its potential as an effective therapeutic approach for managing liver fibrosis and slowing disease progression. A comprehensive review of this field provides valuable insights into its future developments and implications for clinical applications.

KEYWORDS

liver fibrosis, attenuating liver fibrosis, PI3K/Akt pathway, hepatic stellate cells, extracellular matrix

1 Introduction

1.1 Overview of liver fibrosis

Liver fibrosis is a modern condition characterized by the excessive accumulation of ECM proteins in the liver due to chronic injuries (1). These proteins include collagen and alpha-smooth muscle actin (α -SMA), which are highly responsive to liver injuries and can lead to more serious conditions such as cirrhosis and hepatocellular carcinomas. This condition is a global problem, affecting thousands of people. Various factors, including viral infections,

alcohol abuse, autoimmune issues, and NAFLD contribute to the development of liver fibrosis. Understanding the underlying mechanisms and exploring therapeutic techniques is essential for managing this health condition (2, 3).

Mechanistically, liver fibrosis initiates with continual liver injury, and activated HSCs play a crucial role by transforming into myofibroblast-like cells, contributing to ECM production (4). Signaling pathways, particularly the transforming growth factor-beta (TGF- β) pathway, play a pivotal role in regulating ECM synthesis and inhibiting breakdown (5). Chronic inflammation, driven by immune cells releasing pro-inflammatory cytokines, creates a microenvironment that sustains fibrotic processes. The crosstalk among hepatocytes, immune cells, and HSCs influences fibrosis development (6).

On the therapeutic front, the latest approaches focus on inhibiting fibrogenesis. Anti-fibrotic markers targeting HSC activation and ECM production show promising results in both preclinical and clinical research. Immunomodulatory processes and the inhibition of the TGF- β signaling pathway are explored as potential strategies. Addressing metabolic factors, such as obesity and insulin resistance, is gaining attention, and precision medication tailors interventions to individual variations in fibrotic responses (7, 8).

Understanding the mechanisms of liver fibrosis is critical for developing effective therapies. Recent development in anti-fibrotic strategies offers hope for improved patient outcomes and offer avenues for further research and development.

1.2 Overview of PI3K/AKT

The PI3K/AKT intracellular signaling pathway plays a significant role in various cellular processes, including survival, proliferation, metabolism and cell growth. Liver fibrosis is involved the regulation of numerous physiological and pathological conditions (9). The pathway consists of several key components, including protein kinase B (AKT) and phosphatidylinositol 3-kinase (PI3K), which is also referred to as a serine/threonine kinase (10).

PI3K is a lipid kinase that phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 serves as a second messenger and recruits AKT to the plasma membrane, where it is activated by phosphorylation. Activated AKT then phosphorylates downstream targets, leading to the activation of various signaling pathways (11).

Multiple mechanisms regulate the PI3K/AKT pathway to maintain cellular homeostasis. Various extracellular stimuli, such as cytokines, hormones, and growth factors, can be activated. These stimuli bind to their specific receptors and initiate a series of intracellular activity. Furthermore, the tensin homolog PTEN inhibits the AKT activation pathway (12).

In the liver fibrosis context, the PI3K/AKT signaling pathway has been demonstrated to play a significant role in both the attenuation and development of liver fibrotic processes. Examples of chronic liver injury include alcohol abuse, viral hepatitis and NAFLD, all of which can cause hepatic fibrosis. The excessive accumulation of ECM proteins, including collagen, is characterized by the disruption of liver architecture and impairment of liver function in liver fibrosis (13).

2 Components and regulation of PI3K/AKT signaling pathway

The PI3K/AKT signaling pathway is strictly regulated to prevent aberrant activation and maintain cellular homeostasis. Multiple mechanisms control the activity of this pathway, including:

- 1 Activation of RTKs: Receptor tyrosine kinases (RTKs) are transmembrane proteins that cross the cell membrane and bind to specific ligands, such as hormones and growth factors. RTKs undergo autophosphorylation in response to ligand binding, leading to the activation of downstream signaling cascades (14). Ligand binding to RTKs is the main mechanism through which the PI3K/AKT pathway is triggered. The interaction between ligands and receptors induces conformational changes in the receptor, causing autophosphorylation and subsequent activation of downstream signaling (15).
- 2 Negative regulation by PTEN: PTEN, a lipid phosphatase that antagonizes the activity of PI3K by dephosphorylating PIP3, thereby inhibiting downstream signaling through the PI3K/AKT pathway (16). By acting as a negative regulator of the PI3K/AKT pathway, PTEN regulates liver fibrosis. Liver fibrosis can develop as a result of hyperactivation of the pathway caused by mutations in the PTEN gene or loss of PTEN function (17).
- 3 Activation of PI3Ks: RTKs activate PI3Ks, which constitute a family of lipid kinases. Phosphorylinositol 3,4,5-trisphosphate (PIP3) is produced by phosphorylating phosphatidylinositol 4,5-bisphosphate (PIP2) through PI3Ks (18). PIP3 attracts proteins with pleckstrin homology (PH) domains to the cell membrane and acts as a second messenger (1). Upon RTKs activation, PIP2 is phosphorylated to generate PIP3, and PI3Ks are recruited to the cell membrane. The recruitment and activation of downstream signaling molecules depend on this phase (19).
- 4 Activation of Akt: Akt is activated by phosphorylation at two critical sites, Ser473 and Thr308. PDK1 is responsible for mediating phosphorylation at Thr308, whereas mTORC2 is the catalyst for phosphorylation at Ser473. These phosphorylation events are essential for subsequent downstream signaling and Akt activation (20). Akt inhibits GSK3 β , leading to the stabilization of β -catenin and resulting in the downregulation of ECM synthesis (21).
- 5 Negative feedback loops: To prevent excessive activation, the PI3K/AKT pathway is subject to negative feedback regulation. Several proteins, such as the suppressor of cytokine signaling (SOCS) family and insulin receptor substrate (IRS) proteins, can inhibit upstream signaling components, thereby attenuating pathway activity (22).

SOCS proteins regulate cytokine signaling by inhibiting JAK/STAT pathways, while IRS proteins mediate insulin and growth factor receptor signaling. The interplay between SOCS and IRS involves SOCS impacting cytokine pathways, indirectly influencing IRS function and insulin signaling. This dynamic regulation ensures cellular homeostasis in response to various extracellular signals (23).

SOCS and IRS proteins work synergistically in negative feedback loops to modulate the PI3K/AKT pathway (18).

SOCS inhibits upstream signaling components such as Janus kinase (JAK) leading to IRS proteins undergo inhibitory phosphorylation, collectively leading to the attenuation of PI3K/AKT signaling by inhibiting JAK activity, which is upstream of PI3K/AKT pathway. This interference blocks the transmission of signals from cytokine receptors to PI3K/AKT, thus dampening the pathway (24).

In summary, SOCS and IRS act as important modulators in preventing excessive activation of the PI3K/AKT pathway. SOCS proteins provide negative feedback in response to cytokines, while IRS proteins, particularly in the context of insulin signaling, are regulated to ensure proper cellular responses and maintain homeostasis.

A brief outline of the components and regulation of the PI3K/AKT signaling pathway mechanism is depicted in Figure 1.

3 Function of PI3K/AKT signaling pathway in normal physiology

The PI3K/AKT pathway is strictly controlled in normal physiology to ensure appropriate cellular reactions to various stimuli (25).

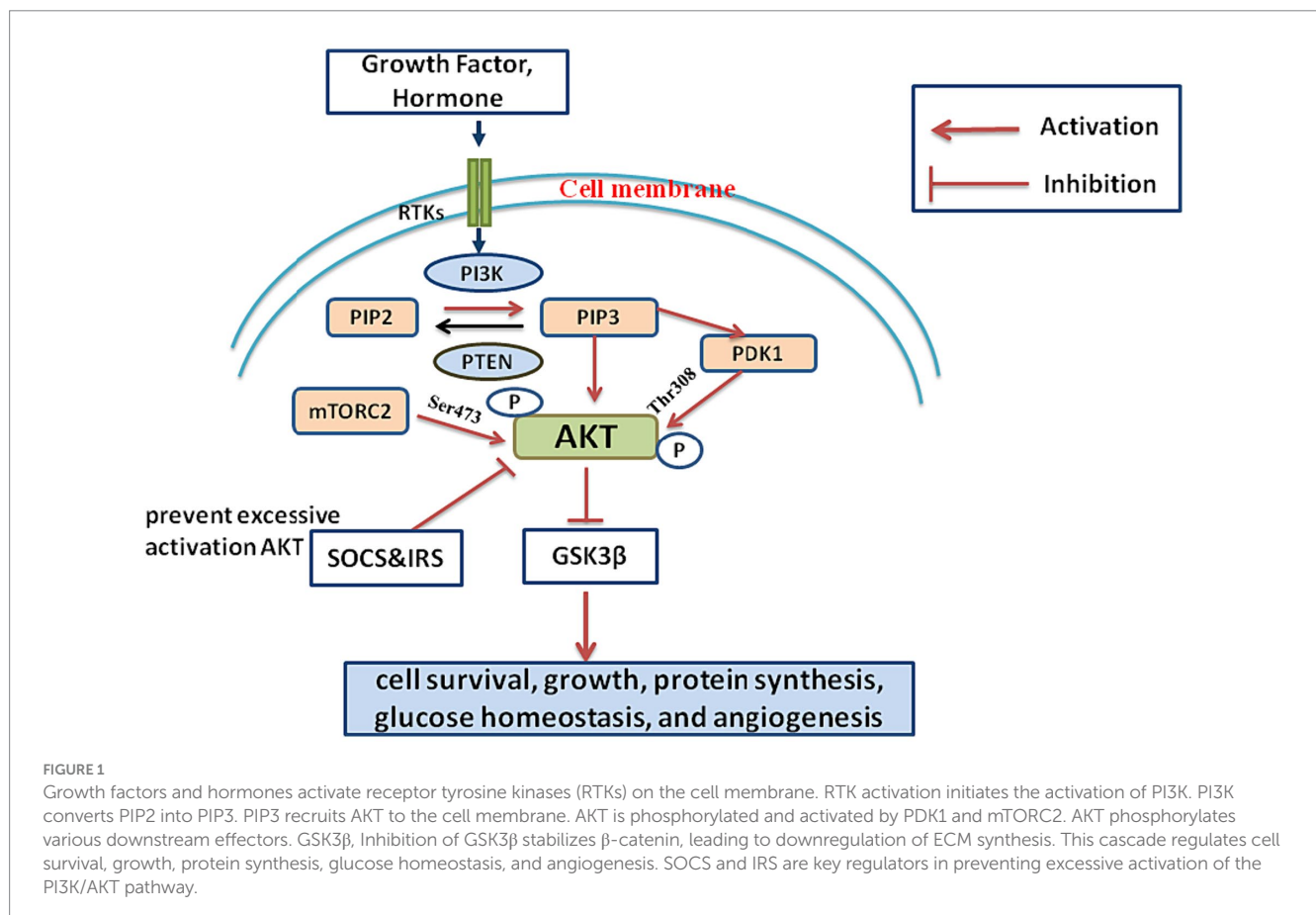
One of the main functions of the AKT pathway in normal physiology is to regulate cell development. Activation of this pathway stimulating protein synthesis and inhibiting apoptosis, promoting cell growth. AKT, the downstream effector of PI3K, phosphorylates and

inactivates pro- apoptotic proteins, such as Bad and caspase-9, thereby promoting cell survival (26).

AKT activation moves glucose transporters, such as glucose transporter 4 (GLUT4), to the cell membrane, promoting glucose absorption and utilization. Increased absorption and consumption of glucose as a result gives cells the energy they require to function. Furthermore, AKT activation promotes the production of glycogen and prevents its breakdown, allowing the body to maintain glucose homeostasis (27).

The PI3K/AKT pathway also plays a role in control of cell proliferation and protein synthesis. Activation of AKT stimulates protein synthesis by activating the mTORC1, a pivotal regulator of protein translation (28).

Activation of mTORC1 leads to the phosphorylation of downstream effectors, including S6K and 4E-BP1, promoting cell growth and protein synthesis (29). Furthermore, by blocking the action of cyclin-dependent kinase inhibitors like p21 and p27, AKT activation advances the cell cycle and permits cell division (30). Angiogenesis is controlled by the AKT/PI3K pathway. Activation of AKT stimulates the synthesis of vascular endothelial growth factor (VEGF) (31). Angiogenesis is largely aided by VEGF, whose production is triggered by AKT activation. This process encourages migration and proliferation of endothelial cell, which results in the creation of new blood vessels (32). Tissue repair and growth, as well as the transport of nutrients and oxygen to tissues, rely on the creation of new blood vessels (15, 25). In Figure 2, the function of PI3K/AKT in normal physiology is outlined.



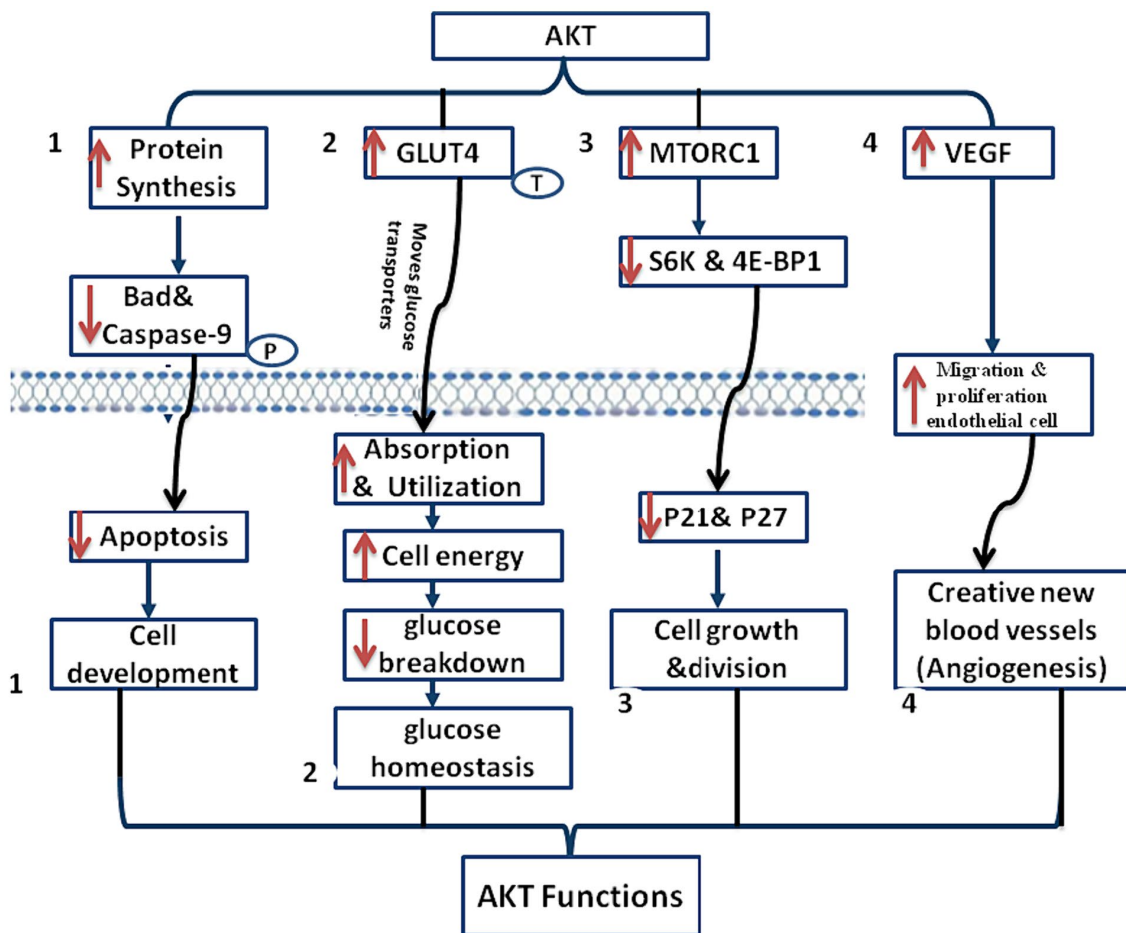


FIGURE 2

This diagram shows AKT/PI3K function, (1) Cell development regulation: AKT pathway regulates cell development by stimulating protein synthesis and inhibiting apoptosis through the phosphorylation of pro-apoptotic proteins like Bad and caspase-9, promotes cell development, (2) glucose homeostasis: AKT activation facilitates glucose homeostasis by enhancing glucose utilization and absorption, ensuring ample energy for cellular functions, and preventing glycogen breakdown, (3) cell proliferation and protein synthesis: AKT promotes cell proliferation and protein synthesis by activating mTORC1, which phosphorylates key effectors (S6K and 4E-BP1), promoting cell growth. AKT activation advances the cell cycle by blocking inhibitors (p21 and p27), permitting cell division, and (4) angiogenesis control: AKT/PI3K pathway controls angiogenesis by stimulating VEGF synthesis, promoting endothelial cell migration and proliferation for the formation of new blood vessels. Essential for tissue repair, growth, and efficient transport of nutrients and oxygen to tissues.

In general, the PI3K/AKT signaling pathway plays a pivotal role in overseeing of the body's normal physiological functions. It governs entire biological processes, ensuring appropriate cellular responses to various stimuli. Dysregulation of this pathway is associated with the development of liver fibrosis. Understanding the functional nature of the PI3K/AKT signaling pathway is essential to elucidating its importance and role in alleviating liver fibrosis.

4 PI3K/AKT signaling pathway in liver fibrosis

Studies have shown that the development and attenuation of liver fibrosis are significantly influenced by the PI3K/AKT pathway, with varying degree of activation observed at different stages of liver disease. The pathway is activated in the early stages of fibrosis,

promoting hepatocyte survival and regeneration. However, as fibrosis worsens, the process is blocked, leading to the overproduction of ECM proteins and the activation of HSCs (33).

There are many ways to attenuate liver fibrosis through the PI3K/AKT signaling pathway. Studies have shown that activation of the pathway can reduce HSC proliferation and activation, decrease ECM production, and promote hepatocyte survival and regeneration. Furthermore, the pathway has the ability to control oxidative stress and inflammatory reactions, which are two major factors in liver fibrosis (8).

The role of the PI3K/AKT signaling pathway in reducing and inducing liver fibrosis has been investigated in several clinical and experimental studies (8). Targeting the pathway for the treatment of liver fibrosis has the potential to yield therapeutic advantages, as shown by these studies. However, further research is needed to fully understand the underlying mechanisms and identify potential therapeutic targets within the pathway (32).

In liver fibrosis, the PI3K/AKT signaling pathway plays a significant role in regulating cellular processes (34). Although AKT pathway activation can mitigate fibrotic processes, dysregulation of the pathway contributes to the onset and progression of fibrosis. Understanding of the pathways via which liver fibrosis is regulated could be helpful in developing new treatment approaches for this debilitating illness (35).

4.1 PI3K/AKT signaling pathway in development of liver fibrosis

The PI3K/AKT signaling pathway plays a crucial role in various biological functions. Understanding its involvement in liver fibrosis has garnered more attention in recent years. Liver fibrosis is characterized by the excessive accumulation of ECM, a progressive condition that impairs liver function and affects liver architecture (36).

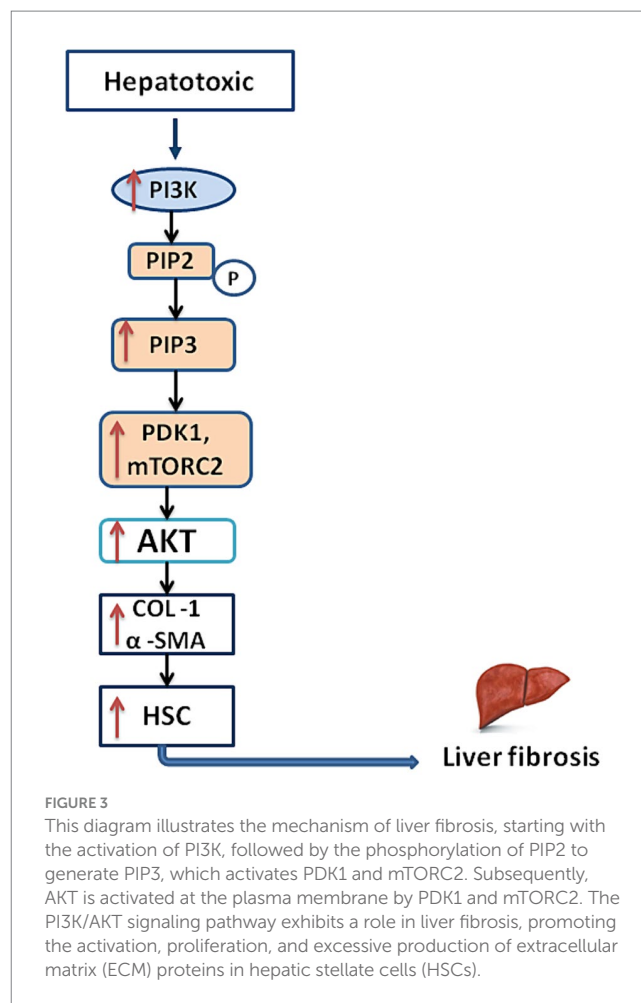
Several cellular function are regulated by the PI3K/AKT signaling pathway, which is activated by cytokines, various growth factors and other extracellular signals binding to cell surface receptors, initiating a series of intracellular events (14). The process begins with the activation of PI3K, which phosphorylates PIP2 to generate PIP3 (37, 38). Subsequently, AKT is recruited to the plasma membrane by PIP3, where it undergoes phosphorylation and activation by PDK1 and mTORC2 (39).

Studies have demonstrated that the PI3K/AKT signaling pathway enhances the activation and proliferation of HSCs, the primary cell type responsible for excessive ECM production in liver fibrosis (40). Increased cell survival, proliferation, and migration in HSCs, along with higher collagen and other ECM protein production, are all outcomes of PI3K/AKT pathway activation. This promotes the growth and worsening of liver fibrosis (41). A brief outline of liver fibrosis mechanism is shown in the Figure 3.

4.2 PI3K/AKT signaling pathway in attenuating liver fibrosis

The PI3K/AKT signaling pathway exhibits a dual function in liver fibrosis, playing roles in both development and attenuation. Regarding the attenuation of liver fibrosis, the pathway emerges as a critical player, offering potential therapeutic avenues for liver cirrhosis. Chronic liver injury triggers the progressive scarring process of liver fibrosis (42, 43).

The reduction of liver fibrosis has also been linked to the PI3K/AKT signaling pathway (44, 45). Numerous investigations have indicated that the activation of AKT decrease the synthesis of collagen, α -SMA, and activation of HSCs, ultimately contributing to fibrosis regression (46). AKT activation inhibits the expression of profibrogenic genes in HSCs, including TGF- β and α -SMA. Additionally, the activated AKT induces the expression of matrix metalloproteinases (MMPs), enzymes involved in ECM breakdown (47). The precise mechanisms by which the PI3K/AKT pathway reduces liver fibrosis are not fully understood. AKT activation leads to inhibition of nuclear factor kappa B (NF- κ B), a transcription factor crucial in inflammation and fibrogenesis (48). This inhibition may be accompanied by a reducing in pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor- α

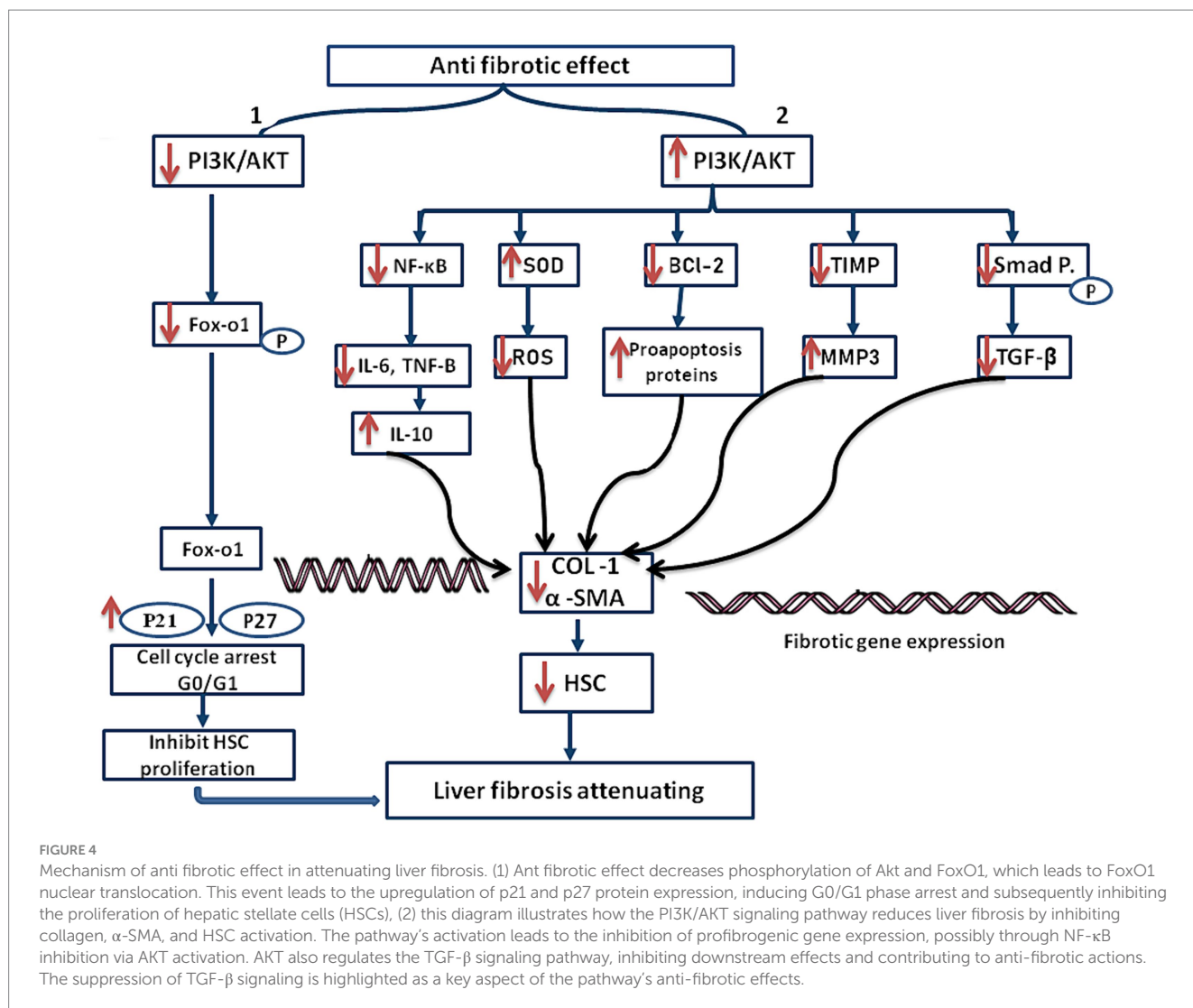


(TNF- α) levels (49). While anti-inflammatory cytokines like interleukin-10 (IL-10) are increased. Suggesting that the activation of AKT improves the resolution of liver fibrosis and reduces the inflammatory response (50).

This inhibition could contribute to the attenuation of liver fibrosis, as collagen production and HSC activation are linked to NF- κ B activation (51). Another potential mechanism is the regulation of the TGF- β signaling pathway by the PI3K/AKT pathway (52). AKT activation inhibits TGF- β signaling by phosphorylating and inactivating Smad proteins, downstream effectors of the TGF- β pathway (53).

The potential role of TGF- β signaling suppression in the anti-fibrotic actions of the PI3K/AKT pathway cannot be overlooked (54, 55). Furthermore, Liver fibrosis is significantly impacted by oxidative stress, characterized by an imbalance between the antioxidant defense system and the generation of reactive oxidative stress (ROS). Studies have shown that the PI3K/AKT signaling system regulates oxidative stress by controlling the production and activity of antioxidant enzyme (56). Activation of AKT leads to increased expression of antioxidant enzymes, such as Superoxide dismutase (SOD) and catalase, which scavenge ROS and protect against oxidative damage (57). The PI3K/AKT pathway attenuates liver fibrosis and promote liver regeneration by regulating ROS (58).

In Addition, apoptosis or programmed cell death, is essential in resolution of liver fibrosis. It has been demonstrated that the PI3K/



AKT signaling pathway causes active HSCs to undergo apoptosis, which facilitates the liver's removal of these cells. Pro-survival proteins, such as Bcl-2 are phosphorylated and rendered inactive during activation of AKT, while pro-apoptotic proteins are stimulated. This change in the ratio of pro-apoptotic to pro-survival proteins triggers the apoptotic cascade, ultimately eliminating activated HSCs and improving liver fibrosis (55, 59).

Besides, Liver fibrosis is characterized by excessive accumulation and inadequate the degradation of ECM proteins. The regulation of ECM remodeling has been linked to the PI3K/AKT signaling system, which modulates the activity of MMPs and tissue inhibitors of TIMPs. Studies have shown that AKT activation enhances MMP production and activity, potentially leading to ECM protein degradation (60).

The PI3K/AKT pathway's role in liver fibrosis extends beyond promotion, with studies indicating its anti-fibrotic effects. Activating the pathway, either pharmacologically using specific agonists or through genetic manipulation, has demonstrated promising results in animal models of chronic liver injury (61). These interventions lead to the inhibition of HSC activation, reduced collagen deposition, and improved liver function (62). The coordination between the pro-fibrotic and anti-fibrotic effects of the PI3K/AKT pathway determines its overall impact on liver fibrosis (61).

In contrast, activation of the PI3K/AKT pathway promotes the activation of HSCs, the main cell type responsible for the production of ECM proteins in liver fibrosis (63). Activated HSCs undergo a process called transdifferentiation, acquiring a myofibroblast-like phenotype characterized by increased proliferation, migration, and production of collagen and other ECM proteins (64). The PI3K/AKT pathway has been shown to promote HSC activation and fibrogenesis through various mechanisms, including the up regulation of TGF-β signaling and the inhibition of apoptosis (62).

While most studies suggest that activating the AKT pathway contributes to the alleviation of liver cirrhosis, contrasting research has shown that inhibiting the AKT pathway also leads to the attenuation of liver cirrhosis. This occurs through the downregulation of Akt/FoxO1 phosphorylation, resulting in the nuclear translocation of Forkhead box protein O1 (FoxO1). Consequently, there is an upregulation of P21 and P27 expression, ultimately causing cell cycle arrest in the G1 phase and effectively inhibits HSC proliferation (28, 65, 66). These divergent findings highlight the current lack of clarity regarding this mechanism, underscoring the need for further elucidation.

A brief outline of the mechanism involved in attenuating liver fibrosis is shown in Figure 4.

TABLE 1 Overview of traditional Chinese medicine targeting the PI3K/AKT pathway to alleviate liver fibrosis.

Compounds	<i>In vitro</i> activity	<i>In vivo</i> activity	Activity in human	References
Xiaoyaosan (XYS)	Not assessed	Yes - rats	Not assessed	(74)
Sini San (SNS)	Yes - HepGz cells	Yes - mice	Not assessed	(75)
Ginsenoside Rh2 (GRHs)	Yes - HSC-TG	Yes - mice	Not assessed	(30)
Corn oligopeptides (COPs)	Not assessed	Yes - mice	Not assessed	(76)
Dahuang Zhechong Pills (DHZCP)	Not assessed	Yes - rats	Not assessed	(77)
Bilberry fruits extract (BEs)	Yes - mouse hepatic AML-12cells	Yes - mice	Not assessed	(78)
Propolis	Not assessed	Yes - male BalB/C mice	Not ASSESSED	(79)
Corydalis saxicola Bunting Total Alkaloids (CSBTA)	Yes - HepG2	Yes - mice	Not assessed	(80)
Ginsenoside Rk3	Not assessed	Yes - C57BL/6 mice	Not assessed	(14)
Arctigenin (ATG)	Yes - HSCs	Yes	Not assessed	(7)
Astragaloside IV (AS-IV)	Not assessed	Yes - rats	Not assessed	(81)
Dihydroartemisinin (DHA)	Yes - HSCs	Yes - rats	Not assessed	(82)
Germacrone (GM)	Yes - HSC- LX-2	Yes - rats	Not assessed	(69)
Gypenosides	Yes - HSCs	Yes - rats	Not assessed	(83)
Songyou Yin (SYY)	Yes - HSCs	Yes - nude mice	Not assessed	(84)
<i>Lycium barbarum</i> polysaccharides (LBPs)	Not assessed	Yes - female rats	Not assessed	(85)
Puerarin	Not assessed	Yes - C57BL/6J mice	Not assessed	(86)
Total alkaloids of <i>Corydalis saxicola</i> Bunting (TACS)	Not assessed	Yes - rats	Not assessed	(87)
Semen Brassicae extract	Not assessed	Yes - Male Sprague–Dawley rats	Not assessed	(34)
Senenoside A (SA)	Yes - HSC-T6 cells	Yes - mouse	Not assessed	(88)
Yu Jin Pulvis (YJP)	Not assessed	Yes - mouse	Not assessed	(89)
Yu Gan Long (YGL)	Not assessed	Yes - rat	Not assessed	(9)
Didymin	Yes - HSCs	Yes - rat	Not assessed	(90)
Silibinin	Yes - LX-2	Not assessed	Not assessed	(91)
Caffeic acid phenethyl ester (CAPE)	Yes - HSC-T6	Yes - male Sprague–Dawley rats	Not assessed	(92)
Ginsenoside Rg2	Yes - HSC-T6	Yes - rat	Not assessed	(38)
Glycyrrhizin (GL)	Yes - splenic CD4(+)T cells	Yes - concanavalin A (ConA)-induced mouse	Not assessed	(93)
Thymoquinone	Yes - T-HSC/Cl-6	Yes - mice	Not assessed	(94)
Berberine	Yes - HSC	Yes - classical mouse	Not assessed	(95)
Tanshinol	Not assessed	Yes - male Sprague–Dawley (SD) rats.	Not assessed	(96)
Curcumin	Yes - HSC	Yes - rats	Not assessed	(97)

5 Interplay of PI3K/AKT and Nrf2 signaling pathway in mitigating liver fibrosis

In the context of liver fibrosis, the PI3K/AKT signaling pathway plays a pivotal role in fibrotic progression, and its interplay with the nuclear factor arylhydrocarbon receptor 2-related factor 2 (Nrf2) pathway introduces an additional layer of complexity to the regulatory mechanisms underlying fibrosis progression. Activation of the PI3K/AKT pathway not only promotes cell survival and inhibits apoptosis but also amplifies Nrf2-mediated antioxidant responses (67). Furthermore, pharmacological modulation of PI3K/AKT signaling augments Nrf2 activity and alleviates liver fibrosis in experimental models (68). A

deeper understanding of the complex crosstalk between these signaling pathways hold promise for the development of targeted therapeutic strategies for effective liver fibrosis management.

6 Investigating PI3K/AKT signaling pathway: clinical insights and experimental evidence

Research studies have shown that the PI3K/AKT signaling pathway plays a vital role in reducing or attenuating liver fibrosis both *in vivo* and *in vitro*. It has been demonstrated that triggering this pathway enhances liver function, inhibit the activation of HSC, and

TABLE 2 Survey of herbal extracts compounds targeting the PI3K/AKT pathway for liver fibrosis alleviation.

Compounds	<i>In vitro</i> activity	<i>In vivo</i> activity	Activity in human	References
Carthami flos extract (CFE)	Not assessed	Yes - mice	Not assessed	(98)
Esculetin	Not assessed	Yes - Wistar rats	Not assessed	(99)
25-OCH ₃ -PPD, a ginsenoside isolated from <i>Panax ginseng</i>	Not assessed	Yes - mice	Not assessed	(100)
Cichorium pumilum Jacq extract (CGEA)	Yes - RAW264.7 cells.	Yes - rats	Not assessed	(70)
Tanshinone IIA (TIIA)	Yes - HSC-LX2	Yes - rats	Not assessed	(101)
Luteolin	Yes - HSCs and HSC-T6 Cell	Yes - mice Sprague–Dawley rats	Not assessed	(102)
Naringin	Not assessed	Yes - rat	Not assessed	(103)
<i>Aronia melanocarpa</i> polysaccharide (AMP)	Not assessed	Yes - TAA-induced liver fibrosis mice	Not assessed	(53)
Lycopene	Not assessed	Yes - rats	Not assessed	(104)

decrease the markers of liver fibrosis. These results demonstrate the therapeutic potential of treating fibrosis by targeting the PI3K/AKT signaling system.

These investigations provide valuable insights into the potential therapeutic possibilities of intervening with this pathway. Researchers have evaluated the impact of PI3K/AKT modulation on liver fibrosis and explored its underlying mechanisms through the scrutiny of both *in vivo* and *in vitro* trials.

In a research conducted by Cai et al. (69), the consequences of PI3K/AKT signaling pathway activation on liver fibrosis were explored using a rat model. Their study revealed that inducing this pathway with a particular agonist substantially decreased liver fibrosis indicators. These results indicate the potential effectiveness of PI3K/AKT activation in mitigating liver fibrosis both *in vivo* and *in vitro*.

Likewise, in an *in vitro* investigation by Han et al. (70), the focus was on the role of the PI3K/AKT signaling pathway in HSC activation, a pivotal step in liver fibrosis development. Their findings revealed that inhibiting the PI3K/AKT pathway using specific inhibitor suppressed HSC activation and decreased the production of fibrotic markers, including CTGF and TGF- β . These outcomes indicate that targeting the PI3K/AKT pathway can inhibit HSC activation and potentially hinder the progression of liver fibrosis.

In another clinical investigation by Baghaei and colleagues (71), the primary focus was on evaluating the therapeutic potential of PI3K/AKT pathway modulation in liver fibrosis patients. The research team conducted a randomized controlled trial where patients were subjected to PI3K/AKT activator treatment for a specific duration. Their observations showed a significant improvement in liver function tests, as well as a reduction in fibrosis markers, such as collagen type III N-terminal peptide and hyaluronic acid. These results suggest that activating the PI3K/AKT pathway may have clinical benefits in ameliorating liver fibrosis in human patients.

Moreover, a study conducted by Li and colleagues (72), explored the effects of PI3K/AKT pathway modulation in the context of liver fibrosis using a cell culture model. In this study, the researchers treated HSC with a PI3K/AKT activator. The result revealed observed a decrease in cell proliferation and collagen production. Additionally, they found that the activated PI3K/AKT pathway inhibited the expression of fibrotic genes, like tissue inhibitor of metalloproteinase-1 and alpha-1 type I collagen. These results provide compelling evidence that PI3K/AKT activation can directly influence fibrotic processes in liver cells.

In another *in vitro* study led by Xiu et al. (73), the researchers investigated the molecular mechanisms underlying the protective attributes of the PI3K/AKT pathway concerning liver fibrosis. Their finding unveiled that activating this pathway inhibited HSC activation and reduced the expression of fibrotic markers, such as CTGF and TGF- β . Furthermore, the researchers observed that PI3K/AKT activation suppressed the nuclear translocation of Smad3, a pivotal mediator in the TGF- β signaling pathway. These findings provide insights into the molecular mechanisms by which the PI3K/AKT pathway mitigates liver fibrosis.

Presented below, Tables 1–5 compile research studies that have investigated the alleviation of liver fibrosis via the PI3K/AKT pathway, including *in vitro* and *in vivo* investigations as well as clinical studies.

MicroRNAs (miRNAs) play a crucial role in attenuating liver fibrosis by targeting the PI3K/AKT pathway. Acting as post-transcriptional regulators, miRNAs modulate key components of the pathway, disrupting the signaling cascade that contributes to fibrogenesis. This regulation mitigates the activation of hepatic stellate cells and the excessive production of extracellular matrix proteins, offering potential therapeutic interventions. Notable studies exploring the role of miRNAs in liver fibrosis and the PI3K/AKT pathway include references (64). These findings highlight the promise of miRNA-based strategies for targeted and personalized therapies against liver fibrosis.

Below is Table 4, featuring two research studies that explored the mitigation of liver fibrosis by targeting the PI3K/AKT pathway using microRNA interventions (Table 5).

7 Conclusion

In conclusion, the PI3K/AKT pathway plays an important role in mitigating liver fibrosis. It acts through multifaceted mechanisms, involving promotion of ECM degradation, inhibition of HSC activation, anti-apoptotic effects, and anti-inflammatory in the liver.

Studies emphasize the therapeutic potential of targeting the PI3K/AKT pathway for liver fibrosis. *In vitro* and *In vivo* studies support its role in improving liver function, ameliorating fibrosis and inhibiting ECM production.

TABLE 3 Summary of chemical compounds targeting the PI3K/AKT pathway for liver fibrosis alleviation.

Compounds	<i>In vitro</i> activity	<i>In vivo</i> activity	Activity in human	References
Adiponectin-based agonist called JT003	Y - HEK293 cells, HepG2 cells, and LX2 cells	Yes - NASH mice	Not assessed	(105)
Aspirin, ticlopidine, and cilostazol	Not assessed	Yes - fisher 344 male rats	Not assessed	(106)
FTY720	Not assessed	Yes - male Sprague-Dawley rats	Not assessed	(107)
Hesperetin	Yes - HepG2 cells	Yes - rats	Not assessed	(33)
Maltol	Not assessed	Yes - mice	Not assessed	(108)
A6	Not assessed	Yes - mice	Not assessed	(109)
Ruangan granules (RGGs)	Not assessed	Yes - rat	Not assessed	(110)
Salvianolic acid A (SA-A)	Not assessed	Yes - rat	Not assessed	(111)
Salvianolic acid B (SAB)	Not assessed	Yes - male C57 mice	Not assessed	(66)
Simvastatin	Not assessed	Yes - male Wistar rats	Not assessed	(112)
Doxazosin	Yes - HCS-LX-2	Yes - mouse	Not assessed	(73)
Artesunate (ART)	HSC- LX-2	Not assessed	Not assessed	(113)
5-BDBD	Not assessed	Yes - C57BL/6J mice	Not assessed	(114)
Nilotinib	Yes - human HCS	Yes - rat	Yes	(89)
Idazoxan	Yes - LX-2	Yes - rat	Not assessed	(67)
Celecoxib	Yes - human HSCs	Yes - rat	Not assessed	(115)
Tenofovir disoproxil fumarate (TDF)	Not assessed	Not assessed	Chronic hepatitis B	(116)
Octreotide	Yes - HSCs	Yes - rat	Not assessed	(117)
JD5037	Not assessed	Yes - rat	Yes - liver fibrosis patients	(118)
Imatinib mesylate (STI-571)	Not assessed	Yes - rat	Assessed	(119)
Pyrazinamide (PZA)	Not assessed	Yes - Sprague-Dawley (SD) rats	Not assessed	(120)
Metformin	Not assessed	Yes - rats	Not assessed	(121)
Metformin	Yes - Cell lines (PLCPRF5 cells)	Yes - NOG mice	Yes - hepatocellular carcinoma (HCC) patients after liver transplantation	(122)
Propranolol	Yes - LX-2	Yes - mouse	Not assessed	(123)
Rapamycin	Not assessed	Yes - rats	Not assessed	(124)
Sorafenib	Not assessed	Yes - rats	Not assessed	(125)
Rimonabant	Not assessed	Yes - rats	Not assessed	(126)
1,8-cineole	Not assessed	Yes - knockout mice	Not assessed	(127)
Actein	Not assessed	Yes - mice	Not assessed	(128)
S-adenosylmethionine (SAM)	Yes - human colon cancer cells	Yes - MAT1A-KO mice	Not assessed	(129)
Sirolimus	Not assessed	Yes - PCK rats	Not assessed	(56)
Vevevisertib	Yes - Hep3B, HepG2, Huh7, and PLC/PRF cell lines	Yes - rats	Not assessed	(130)
Quercetin	Not assessed	Yes - mice	Not assessed	(131)
Resveratrol (RSV)	Yes - HSC-T6 cells	Yes - rat	Not assessed	(132)
Dihydromyricetin (DHM)	Not assessed	Yes - mice	Not assessed	(133)
Hemistepsin A (HsA)	Yes - HSCs	Yes - male ICR mice	Not assessed	(134)
Asiatic acid (AA) isolated from <i>Centella asiatica</i>	Not assessed	Yes - Rat	Not assessed	(135)
Cytisine derivatives, including compound 5f	Human LX-Cell	Not assessed	Not assessed	(136)
Atractylenolide III (ATL III)	Not assessed	Yes - mice	Not assessed	(137)
Tormenteric Acid (TA)	Not assessed	Yes - Rat	Not assessed	(138)

(Continued)

TABLE 3 (Continued)

Compounds	<i>In vitro</i> activity	<i>In vivo</i> activity	Activity in human	References
Taxifolin	Not assessed	Yes - mouse	Not assessed	(139)
Honokiol	Yes - AML-12 hepatocytes	Yes - mouse	Not assessed	(140)
Hovenianin A	Yes - HSCs	Not assessed	Not assessed	(141)
Epigallocatechin-3-gallate (EGCG)	Yes - human HSC-XL-2	Yes - bile duct-ligated (BDL) rats.	Not assessed	(142)
Isovitexin	Not assessed	Yes - mice	Not assessed	(143)
Alpha mangostin	Yes - HSC	Not assessed	Not assessed	(144)
Hesperitin derivative-11 (HD-11)	Yes - HSC-T6 cells	Yes - rats	Not assessed	(145)
Matrine derivative WM130	Yes - HSC-IL-2	Yes - rats	Not assessed	(146, 147)

TABLE 4 Summary of microRNAs targeting the PI3K/AKT pathway for attenuating liver fibrosis.

Compound	<i>In vitro</i> activation	<i>In vivo</i> activation	Human activity	References
miR-29b	Yes - LX-1 and HSC-T6 cells	Yes - mouse	Yes assessed	(64)
miR-101	Yes - HSC-LX-2	Yes - mouse	Not assessed	(148)

TABLE 5 Summary of biological compounds targeting the PI3K/AKT pathway for attenuating liver fibrosis.

Compound	<i>In vitro</i> activation	<i>In vivo</i> activation	Human activity	Reference
Erythropoietin (EPO)	Not assessed	Yes - rat	Not assessed	(149)

The pathway's beneficial effects are intricate and entail the modulation of several downstream signaling pathways, including GSK-3 β , mTOR and FOXO3a, which impact apoptosis, cell proliferation, and metabolism.

The PI3K/AKT signaling pathway is a promising target for liver fibrosis therapy, with potential therapeutic candidates, including AKT and PI3K isoforms, as well as downstream effectors, showing encouraging prospects and preclinical results for future clinical use.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

Protein kinase B	AKT
Phosphoinositide 3-kinases	PI3Ks
phosphatidylinositol 4,5-bisphosphate	PIP2
phosphatidylinositol 3,4,5-trisphosphate	PIP3
Extracellular matrix	ECM
Hepatic stellate cells	HSCs
phosphoinositide-dependent kinase 1	PDK1
Mammalian target of rapamycin complex 1	mTORC2
Matrix metalloproteinases	MMPs
Pleckstrin homology	PH
Phosphoinositide-dependent kinase 1	PDK1
Glucose Transporter 4	GLUT4
Vascular endothelial growth factor	VEGF
Reactive oxygen species	ROS
Superoxide dismutase	SOD
Ribosomal protein S6 kinase	S6K
Eukaryotic initiation factor 4E-binding protein 1	4E-BP1
Interleukin- 6	IL-6
Interleukin- 10	IL-10
Tumor necrosis factor-alpha	TNF- α
Non-alcohol fatty liver disease	NAFLD
alpha-smooth muscle actin	α -SMA
B-cell lymphoma 2	Bcl-2
Glycogen Synthase Kinase 3 Beta	GSK3 β
Tissue Inhibitors of Metalloproteinases	TIMPs
Suppressor of cytokine signaling	SOCS
Insulin receptor substrate	IRS
Phosphatase and Tensin	PTEN