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Combination Therapy with Vitamin D and Telmisartan to Suppress the Progression of Liver Fibrosis.

Review Article

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ABSTRACT

Hepatic fibrosis is an improper wound repair response associated with various kinds of chronic liver injuries. It can be detected by over-deposition of diffuse ECM (Extracellular Matrix) and abnormal overgrowth of connective tissue, and it can progress to cirrhosis or hepatocellular carcinoma. Chronic liver diseases, which include liver fibrosis, have resulted in significant morbidity and mortality worldwide, and this trend is likely to continue. Although early liver fibrosis has been reported to be reversible, the exact mechanism of reversal is unidentified, and there is a lack of effective therapy for liver fibrosis. Vitamin D is essential for maintaining the metabolism of bone and calcium balance. Unexpectedly new evidence indicates that vitamin D has a protective function toward hepatic fibrosis. Telmisartan has been shown to have a positive effect on hepatic fibrosis markers in various pathological contexts. This review focused on summarizing the effect of vitamin D and telmisartan on the progression of hepatic fibrosis and updating their present impact on fibrosis. Telmisartan and vitamin D reduce fibrosis in hepatic stellate cells by inhibiting the production of profibrogenic genes.

Keywords: Liver fibrosis, Vitamin D, Vitamin D receptor, Telmisartan

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INTRODUCTION

The liver is the most essential organ in humans, it is necessary for many processes like the metabolism of energy, toxic substance elimination, and control of the immune system. Because of these intensive functions, the liver is susceptible to a variety of diseases, including viral infections, autoimmune diseases, malnutrition, and alcoholism. Continuous damage to the liver has been shown to result in hepatic fibrosis. [1, 2].

Liver Diseases

The liver, as the primary organ for detoxification and metabolization, is vulnerable to a variety of illnesses. Liver disease rates have progressively risen throughout the years. According to WHO, chronic diseases cause approximately 46% of the world's diseases and 59% of mortality, with nearly 35 million people dying worldwide [3]. Several major diseases of the liver can lead to inflammation. This inflammation can lead to scarring or cirrhosis.

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Diseases can be classified as either acute or chronic [4]. There are numerous types of liver disease, which can be a consequence of a virus, medication or chemical destruction, obesity, diabetes, or an immune system attack. They are classified as hepatic steatosis, jaundice, hepatitis, fibrosis, cirrhosis, cholestasis, and carcinoma, as indicated in ***Figure 1*** [5].

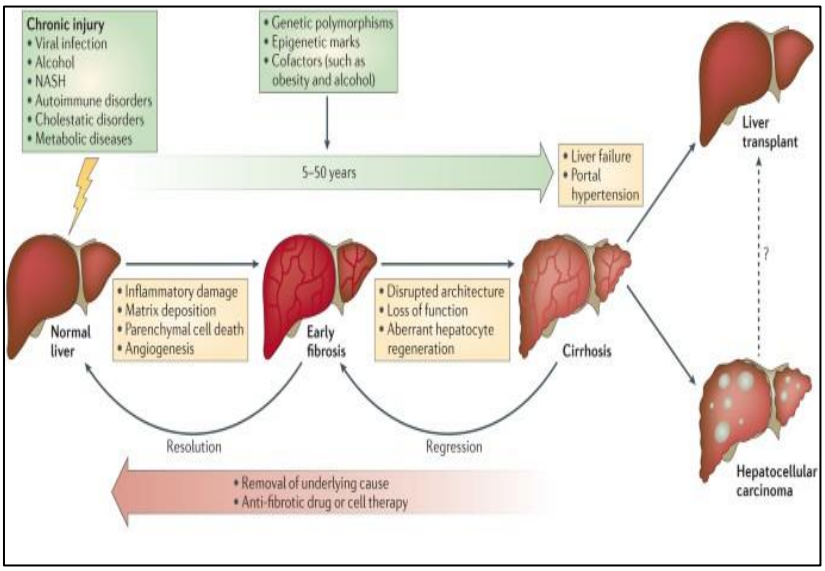

Figure 1. **Chronic hepatic diseases development** [6]

Liver fibrosis

Hepatic fibrosis is a serious disorder that may result in cirrhosis and liver cancer. There are several types of chronic liver damage, like viral infections, cholestatic diseases, consumption of alcohol, nonalcoholic steatohepatitis, and non-alcoholic fatty liver disease, which may result in inflammation of the liver and abnormal wound healing process, resulting in fibrosis [7]. Hepatic fibrosis can be recognized by excessive accumulation of extracellular matrix (ECM) and formation of fibrous scar. degradation of liver structure by fibrous scars and the loss of hepatocytes could inhibit the biological functions of the liver, leading to liver failure [8]. The evaluation of fibrosis allows significant information and is highly helpful for the diagnosis, in addition to the treatment strategy and evaluating the natural history or progression during therapy. [9].

The pathological process of Liver Fibrosis

Alcoholism, metabolic problems, viral infection, obesity, steatosis, and cholestasis are all risk factors for liver fibrosis, with abuse of alcohol being the most common. Throughout the metabolism of alcohol, acetaldehyde, and ROS (reactive oxygen species) are formed. Acetaldehyde stimulates TGF-β synthesis and type I collagen production in HSCs, leading to liver fibrosis [10, 11]. The pathogenic liver fibrosis process mostly involves the accumulation of collagen and proteins of ECM in fibroblasts that trigger wound repair responses [12]. Myofibroblast stimulation and proliferation are the most common causes of fibrous collagen and the deposition of ECM in the injured liver. During HSC activation, Myofibroblasts are produced and released from portal fibroblasts, bone marrow-derived fibroblasts, mesenchymal cells, and liver parenchyma-derived myofibroblasts by epithelial-mesenchymal

transition (EMT), resulting in a major portion of the liver fibrosis [13].

Pathogenesis of liver fibrosis determines which different types of myofibroblasts develop. Previous research has shown that the primary source of myofibroblasts in the hepatic fibrosis model induced by CCl_4 is HSCs. In the cholestatic liver, portal fibroblasts generate myofibroblasts, while in chronic harm, bone marrow-derived cells contribute to the total fiber-derived differentiation [14-16]. Progression of liver fibrosis is mainly controlled by different cells and cytokines, and HSC activation is considered the main link of hepatic fibrosis [17, 18].

HSCs are located in the subcutaneous space surrounding the liver's sinuses, among hepatocytes and blood sinus endothelial cells. In normal physiological processes, HSCs are in dormancy and store fat and fat-soluble vitamins. In liver damage, HSCs are triggered by inflammatory mediators, which then divide into myofibroblasts. After that, HSCs release proteins of ECM and matrix metalloproteinases, which result in remodeling of liver tissue. progression of hepatic fibrosis can be seen in ***Figure 2*** [19]

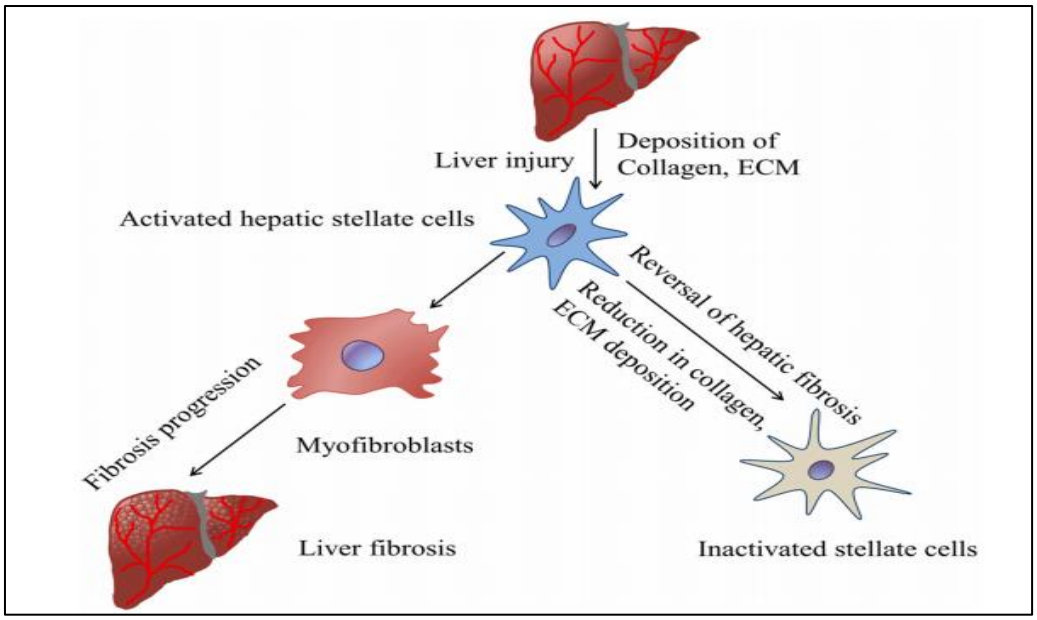

***Figure 2*. Development and reversal of hepatic fibrosis.** [20]

Diagnosis of hepatic fibrosis

Precise diagnosis of the degree of hepatic fibrosis is required for medical therapy to assess the prognosis and treatment decisions among patients [21]. Despite the development of possible diagnostic procedures over the last 50 years, biopsy is regarded as the gold-standard technique for assessing fibrosis and provides helpful details about diagnosis and other harmful processes such as necrosis, inflammation, and steatosis [22]. The Ishak score, Metavir score, and Desmet/Scheuer staging system are three commonly applied for assessing histological fibrosis [23].

The scoring system depends on the progression of periportal fibrosis, after septal fibrosis, followed by nodule formation [24]. One of the liver biopsy limitations is its high invasiveness. Furthermore, low quality of the sample and tissue size result in non-reproducible biopsy, and it is dependent entirely on the pathologist's knowledge, resulting in

interobserver variations. Due to the drawbacks of liver biopsy, a noninvasive method for diagnosing liver fibrosis was developed. A suitable biomarker should be organ-specific, sensitive to detecting active damage, easily accessible in peripheral tissue, and inexpensive [25].

The advantages of biomarkers in comparison to liver biopsy are that they can be estimated in serum using a minimally invasive method. Additional benefits include ease of use, inter-laboratory reproducibility, and widespread availability. Serum biomarkers of hepatic fibrosis can be categorized into 2 different groups: direct biomarkers, which indicate turnover of ECM, and indirect biomarkers, which are released into the blood and indicate changes in hepatic function [26]. Indirect markers indicate changes in liver function. These markers may assist with liver disease diagnosis, severity evaluation, therapy monitoring, and prognosis assessment. Measuring enzyme activity, including levels of aminotransferases, alkaline phosphatase (ALP), and γ-glutamyl transferase (γGT), and also estimating bilirubin and albumin in the blood [27, 28].

Direct markers play a direct role in the accumulation of ECM made by HSC and other hepatic cells. Levels of these markers in serum are increased in the progression of fibrosis and tend to decrease during therapy [9]. these markers Evaluation may be beneficial in determining efficient therapy. Direct markers can be categorized by their molecular structure [29].

Treatment of hepatic fibrosis

The present therapies for liver fibrosis attempt to eliminate related damage factors by inhibiting hepatic stellate cells (HSCs) activation, promoting ECM destruction, and preventing inflammatory reactions [30, 31]. Currently, there are no approaches to treating liver fibrosis or early cirrhosis in clinics other than conventional drug therapy. Conventional therapies have some drawbacks for tissues and organs, including toxic effects and side effects, in addition to Drug specificity is low, this prevents therapeutic drugs from being effectively concentrated in the liver. As a consequence, their efficacy for treatment is not desirable[32]. As a result, the article's primary goal was to assess vitamin D and telmisartan's beneficial effects on the progression of hepatic fibrosis, focusing on their critical mechanisms controlling liver fibrosis. Furthermore, we sought to summarize the current state of their treatment in hepatology. Particularly, approaches for both early detection and therapy of liver fibrosis.

Role of Vitamin D in liver fibrosis

Vitamin D is a steroidal hormone that plays a major role in maintaining calcium and bone balance. [33]. Besides its traditional effect on the health of bones, it has a biological effect on many types of cells, resulting in control of proliferation and differentiation of cells [34]. Vitamin D is available in 2 equivalent types: vitamin D_2 and vitamin D_3, each of which can be obtained through diet.

Vitamin D_2, or ergocalciferol, is produced in certain kinds of plants but primarily in fungal organisms through UVB (ultraviolet B) activity on ergosterol. In humans, the skin produces the greatest amount of vitamin D3 through UVB rays from sunlight. In the lower epidermis, 7-dehydrocholesterol (DHC) is converted to pre-vitamin D_3. A thermal-dependent isomerization process converts pre-vitamin D_3 into vitamin D^3 (cholecalciferol) [35]. Telipophilic cholecalciferol is non-bioactive. It must also go through two sequential hydroxylation in the liver and kidney to become an intermediate metabolite and then reach its final active form. In the blood, cholecalciferol is primarily linked to vitamin D-binding protein (DBP) or albumin before reaching the liver for 25-hydroxylation. 25-OHD_3 is commonly used for determining systemic vitamin D levels. In the kidney's proximal tubule, 25(OH)D-1α-hydroxylase enzyme, or CYP27B1, turns 25(OH)D_3 to its active type [36].

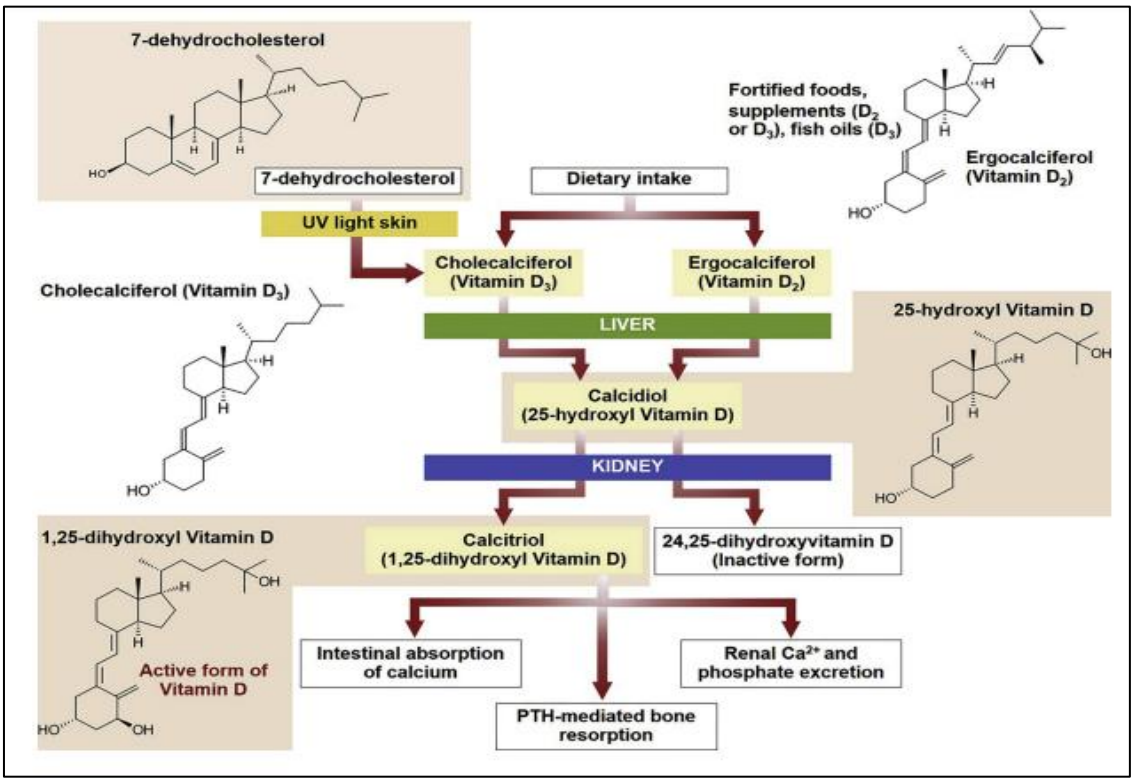

Figure 3. **Vitamin D Biosynthesis [37].**

Vitamin D effect on liver diseases

Vitamin D helps to reduce the risk of chronic diseases such as diabetes, cancer, and other heart disease, autoimmune, and infectious diseases. the effect is due to the synthesis of 1α,25(OH)2D, which has autocrine and paracrine processes in proliferation and differentiation and cell death [36, 38]. Recently, vitamin D plays an essential part in maintaining the fibrotic process, inhibiting collagen synthesis in stromal HSCs. Additionally, data are building up to support the theory that vitamin D-mediated VDR activity could be involved in the reduction of fibrosis. For instance, current research by Ding et al. [37] VDR enhances Unexpected fibrosis of the liver.

The vitamin D/VDR direction inhibits TGF-β-induced fibrosis of the liver in HSCs by attaching with regulatory loci of pro-fibrotic genes which decrease SMAD-3 recruitment. This VDR/SMAD genomic feedback process regulates fibrosis. In Abramovitch et al. [39] research, They discovered the anti-fibrotic activity of vitamin D in HSCs by responding to VDR, implying a possible physiological effect on VDR-mediated fibrosis. But Neeman et al. [40] found that farnesylthiosalicylic acid and vitamin D had a beneficial impact on HSCs by the Ras-guanosine-5′-triphosphate (GTP) and phospho-extracellular signal-regulated kinase (pERK) signaling pathways. Artaza and Norris showed that vitamin D reduces TGF-β by blocking many pro-fibrotic proteins.

Vitamin D inhibits the production of collagen I and III was inhibited by vitamin D while increasing the production of MMP-8 [41]. A metalloproteinase plays an important role in restricting extracellular matrix destruction that is linked to the development of fibrogenesis. Activating TGF-β/SMAD-3 promotes fibrosis by transforming HSCs and secreting a matricellular protein involving connective tissue growth factor at the destruction of ECM [42]. in rats, CTGF synthesis was significantly raised; but after vitamin D medication, its levels significantly dropped [43]. the results demonstrate that there is an important role of vitamin D-mediated

CTGF expression in the progression of fibrogenesis [44].

Results from in vitro and in vivo research further indicate vitamin D's protective role in fibrogenesis. Recently, Beilfuss et al. [45]. discovered that vitamin D/VDR inhibits TGF-β-induced pro-fibrogenic gene expression in HSCs. Also, there is a correlation between VDR and fibrosis among nonalcoholic fatty liver disease patients as shown in ***Figure 4.***

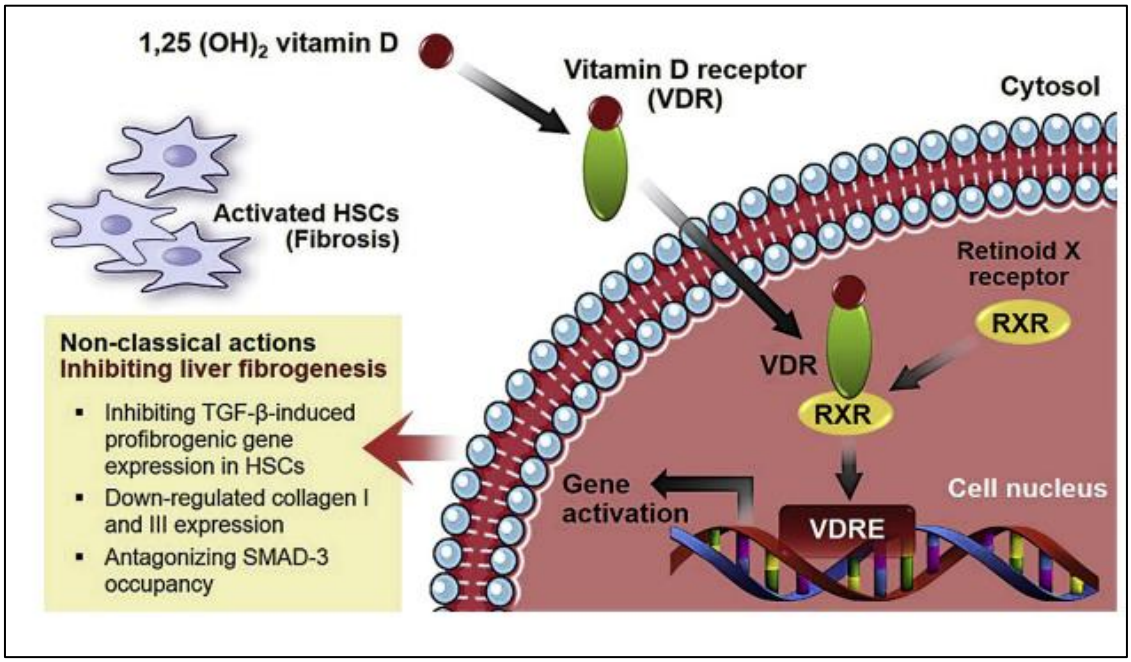

Figure 4. **Vitamin D and hepatic fibrosis [37].**

These consequences have an important part in chronic liver diseases. Deficiency of Vitamin D is particularly known among individuals who have chronic liver disease. 93% of these people have vitamin deficiency [46, 47]. Even those with mild liver disease are affected. Patients suffering from liver diseases. Up to 93% of these patients have some level of vitamin deficiency. Multiple investigations demonstrated that tiny amounts of 25(OH)D increase the chance of mortality, involving heart disease [48].

Role of Telmisartan in liver fibrosis

Telmisartan is a particular angiotensin receptor blocker (ARB) that regulates PPAR-γ activity, enhancing insulin sensitivity and reducing hepatic fat building up [49], Furthermore, blocking the angiotensin II receptor prevents activation of HSC, so it reduces fibrosis [50, 51]. Telmisartan decreases hepatic damage caused by type 1 diabetes mellitus [52], Combined with propranolol, it decreases signals of fibrosis like hydroxyproline, bile duct development, procollagen-α1, endothelin-1, and metalloproteinases in a PSC-like mouse model [53]. It additionally prevents fibrosis in the rat bile duct ligation model [54].

Telmisartan reduces liver inflammation and fibrosis in rats who nourished a fatty diet and provided a small dosage of streptozotocin (STZ) just two days after birth [55]. It acts as an angiotensin receptor blocker that treats hypertension. Telmisartan (Micardis®; Boehringer Ingelheim, Ingelheim, Germany) is a nonpeptide ARB with orally active properties that are linked to AT1 receptors, preventing angiotensin II's biological effect. It has a bis-benzimidazole structure, as illustrated in ***Figure 5***.

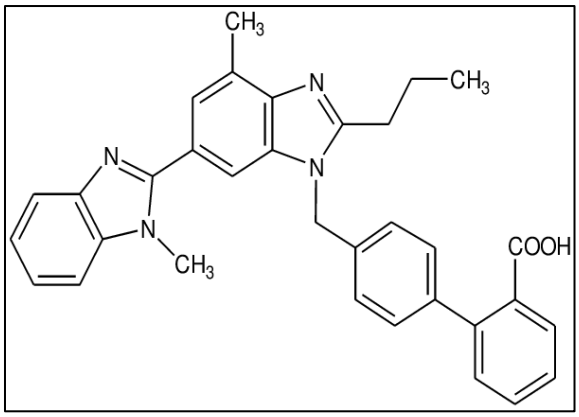

Figure 5. **Chemical Structure Of Telmisartan [56].**

Additionally, it is helpful for hypertension, improving the sensitivity of insulin in diabetes Type 2, and lowering triglycerides. Telmisartan can be used to treat NASH with metabolic syndrome, as the majority of NAFLD patients have metabolic syndrome features [57]. ARBs have been widely recognized as a method of blocking the contraction of blood vessels and inhibiting the growth of cells and fibrogenesis which is controlled via the angiotensin II type 1 receptor (AT1-R) [58]. AT1-R knockout mice exhibited lower levels of hepatic TGF-β1 and pro-inflammatory cytokines in comparison to WT mice. Moreover, Bataller et al [59] .

Bataller et al[61] found that elevated systemic Angiotensin (Ang) II levels cause fibrogenesis and promote inflammation. Telmisartan has the strongest attachment for the AT1-R and has an extremely long duration of half-life among the ARBs [60]. Furthermore, Telmisartan's lipophilicity and preference for the liver make it ideal for liver signs [60]. The angiotensin-converting enzyme (ACE) 2/Ang (1-7) process was investigated just like a substitute to that of the RAS [61]. The stimulation of Mas, the G-protein-coupled Ang (1-7) receptor, induces vasodilation and antifibrotic signaling pathways in heart myocytes [62]. In this process, ACE2 changes Ang II to Ang (1–7) and Ang I to Ang (1–9) [63]. Telmisartan has been shown to improve hepatic fibrosis markers in various destructive contexts [64].

Telmisartan's therapeutic impact on hepatocytes can be linked to its anti-oxidative properties [51]. likewise, telmisartan decreased liver fibrosis that was triggered in rats by diet with methionine-deficient and choline-deficient [65]. Telmisartan affects the production of PPAR-γ target genes that regulate the metabolism of carbohydrates and lipids. It has been demonstrated to decrease levels of glucose, insulin, and triglyceride in animals fed a high-fat, high-carbohydrate diet [49]. PPAR-γ improves insulin sensitivity, and high-density lipoprotein levels, and reduces levels of inflammation, oxidative stress, cell migration and proliferation, and fatty acid and triglyceride. However, it does not cause accumulation of fluid like full agonists of PPAR-γ, such as pioglitazone or rosiglitazone [51] as shown in ***Figure 6.***

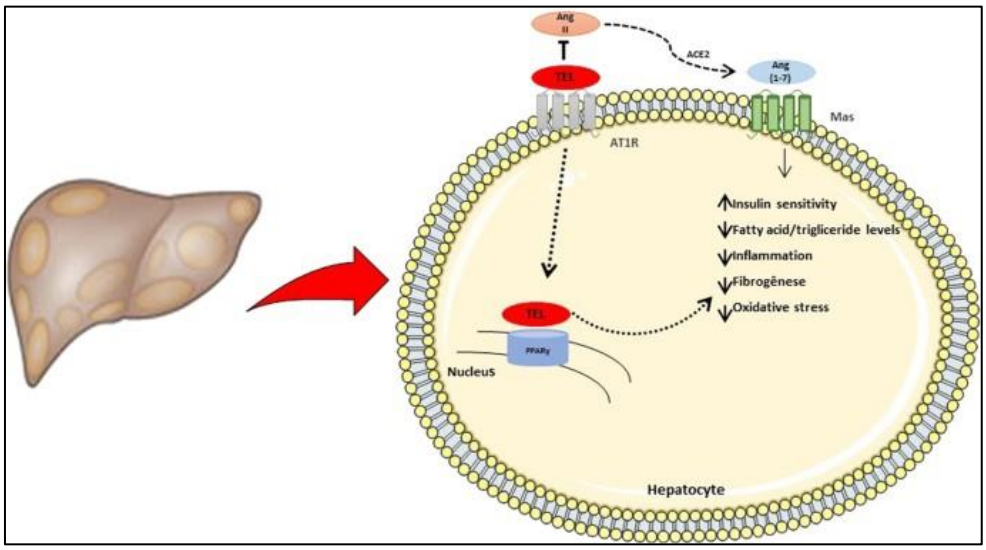

Figure 6. **The liver-protecting actions of telmisartan in liver diseases are shown [66].**

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