# Tissue fibrosis, aging and the potential use of cannabinoids as anti-fibrotic agents

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## Abstract

Fibrosis is a condition characterized by thickening or/and scarring of various tissues. Fibrosis may develop in almost all tissues and organs, and it may be one of the leading causes of morbidity and mortality. It provokes excessive scarring that excels the usual wound healing response to trauma in numerous organs. Currently, very little can be done to prevent tissue fibrosis, and it is almost impossible to reverse it. Therefore, fibrosis is frequently associated with premature aging. In turn, aging is associated with more frequent incidences of fibrosis. Anti-inflammatory and immunosuppressive drugs are among the few treatments that may be efficient in preventing fibrosis. Numerous publications suggest that cannabinoids and extracts of *Cannabis sativa* have potent anti-inflammatory and anti-fibrogenic properties. In this review, we describe the types and mechanisms of fibrosis in various tissues and discuss various strategies for prevention and dealing with tissue fibrosis. We further introduce cannabinoids and their potential for the prevention and treatment of fibrosis, and therefore for extending healthy lifespan.

**Keywords:** fibrosis; medicinal plants; Cannabis sativa; cannabinoids; anti-fibrotic

## Introduction

Aging is the process of the progressive accumulation of minute changes making an organism more susceptible to disease and death as a result. Many pathological processes are more frequent with age, including fibrosis. In addition, fibrotic changes in various tissues accelerate aging and frequently cause a premature death.

Fibrotic illness is not well explored, it has a poor outcome and is mainly untreatable, all of which is compared to the terminal stage of cancer.(Wernig et al. 2017) Fibrosis is defined as an excessive growth, stiffness, and sometimes scarring of different tissues or organs along with an imputed overaccumulation of extracellular matrix components and collagen.(Y. Liu 2011) This condition is a lifelong pathological anomaly that may occur in various organs (Table 1), with a higher frequency in the skin, liver, heart, kidneys, lungs.

Aging is a predisposing factor for fibrosis development. The accumulation of the trauma and stress happening over a lifetime expedites biological aging. (Murtha et al. 2019)

Different types of fibrosis have been recognized based on anatomical location such as pulmonary (Idiopathic pulmonary fibrosis, Cystic fibrosis, Emphysema), liver (Cirrhosis, Portal hypertension, Hepatocellular carcinoma) or skin (Keloids, Systemic sclerosis). The most well-known and studied example of fibrosis is Idiopathic Pulmonary Fibrosis (IPF). This condition is a lifelong, incurable illness targeting lungs. This disease usually affects middle-aged people and older adults and is characterized by a long-lasting cough along with difficulties in breathing of an unknown origin; besides IPF is very difficult to diagnose. Because of the pure life expectancy and insensitivity to pharmacological treatments, IPF is very common nowadays. An average survival time is three years. Many IPF patients struggle with an acute worsening of breathing that is correlated with high mortality.

The progression rate of this condition is very unpredictable. Some patients can deteriorate very quickly, while others may remain asymptomatic for many years. There is no generally approved treatment for this disease. The development of treatments is focused on fibroproliferation and fibrogenesis. (Y. Liu 2011)(Hoyer et al. 2019)(Fujimoto, Kobayashi, and Azuma 2015)

**Table 1. Main types and causes of fibrosis**

| Organ/tissue | Type of fibrosis |
|---|---|
| Skin | Hypertrophic scar<br>Systemic sclerosis |
| Heart | Cardiac fibrosis<br>Hypertrophic cardiomyopathy<br>Cardiac dysfunction<br>Valvular disease<br>Arrhythmia |
| Bone marrow | Myelofibrosis<br>Myelodysplastic syndrome<br>Chronic myelogenous leukemia |
| Liver | Cirrhosis<br>Portal hypertension<br>Hepatocellular carcinoma |
| Retroperitoneum | Retroperitoneal fibrosis |
| Gut | Intestinal fibrosis<br>Enteropathies<br>Inflammatory bowel disease |
| Joint | Arthrofibrosis |
| Brain & Nervous system | Glial scar<br>Alzheimer |
| Eye | Subretinal fibrosis<br>Epiretinal fibrosis<br>Vision loss |
| Lung | Idiopathic pulmonary fibrosis<br>Cystic fibrosis<br>Pulmonary hypertension<br>Thromboembolic disease<br>Emphysema |
| Mediastinum | Mediastinal fibrosis |
| Pancreas | Pancreatic fibrosis<br>Cystic fibrosis<br>Chronic pancreatitis<br>Duct obstruction |
| Kidney | Renal fibrosis<br>Cystic fibrosis<br>Nephrogenic systemic fibrosis<br>Chronic kidney disease<br>Renal anemia |

Epidemiological data on fibrosis in different organs is well documented in the literature. For example,

an incidence of idiopathic pulmonary fibrosis varies between 0.6 and 17.4 per 100,000 population per year (Ley and Collard 2013), two third of all patients were 60 years and above, and the highest prevalence was reported among patients of 80 years and above - 165.9 per 100,000 population. (Raimundo et al. 2016) In Caucasians, cystic fibrosis occurs roughly in 1 in 3,000-4,000 births; and among other races, cystic fibrosis is less frequent, 1 in 4,000-10,000 in Latin Americans and 1 in 15,000 – 20,000 in African Americans, and even less in Asian Americans.(Lakhani 2019) As to liver cirrhosis, according to 2017 data, 112 million compensated cases were reported worldwide (Sepanlou et al. 2020), and in patient who were more than 65 years old, a risk of severe liver fibrosis was 3.78 times higher (Kim, Kisseleva, and Brenner 2015). Also, more than 100 million cases of keloid are reported annually worldwide.(Gauglitz et al. 2011)(Li et al. 2017)

**Etiology of inflammation**

Exposure to some pulmonary system pathogens and airborne pollutants can lead to premature aging. (Murtha et al. 2019) There are two types of inflammation factors, infectious and non-infectious. Examples of the first group include viruses, bacteria, and/or other microorganisms. Non-infectious factors can be subdivided into biological, chemical, physical, and psychological ones. The injured cells are an example of a biological subtype. Chemical examples are alcohol, chemical irritants, fatty acids, and glucose. Another category includes physical factors such as burns, frostbites, foreign bodies, ionizing radiation, physical trauma, and injuries. The final agent is psychological excitement.(Chen et al. 2018)

**Pathogenesis**

There are two ways of repair of the injured tissues. The first one is the regeneration by the propagation of undamaged cells and the maturation of stem cells. The second one is scar tissue formation through the accumulation of connective tissues. The regeneration is a possibility of damaged tissues to be repaired and their defective elements to be restored. Cells that remain undamaged are able to proliferate and maintain a constant quantity. In some cases, fibrosis may occur due to a critical tissue injury or as a result of the inability of injured tissue to accomplish the repair. Fibrosis occurs due to either a large amount of collagen deposition associated with the long-lasting inflammation or ischemic necrosis. The scar formation and regeneration are associated with the growth of different cells and a strong communication between them and the extracellular matrix (ECM). Cell proliferation is handled by growth factors, although the central role is played by ECM and maturation of stem cells. (Occleston et al. 2010)

There are different types of cells, such as fibroblasts, vascular endothelial cells, and some fragments of injured tissues that proliferate along with the repair of damaged tissues. Tissue repair is characterized by the proliferation of connective tissues rather than parenchymal tissues, which leads to fibrosis and scarring. In contrast, the regeneration is characterized by the proliferation of parenchymal cells. Therefore, there is a substantial difference between regeneration and repair. (Galliot et al. 2017)

Tissues may be classified by the proliferative capability. (Krafts 2010) The information about a cell cycle will help interpret this classification. The cell cycle is a period between two eukaryotic cell divisions; and there are four main phases $G_1$, S, $G_2$, M. The cell cycle starts from $G_1$ (Gap 1 phase) in the time during which cells synthesize proteins and mRNA. The $G_1$ phase is followed by the S phase during which DNA replication occurs. The third phase is $G_2$, the phase during which cells continue the synthesis of proteins and RNA, prepare for a mitotic division, growth, and check for any errors. During the M phase, mitosis occurs, and the cell divides into two daughter cells.(Kousholt, Menzel, and Sørensen 2012)

The first group in the proliferative classification are labile cells (continuously dividing cells) which

regularly die and can be restored with the help of tissue stem cells. They can regenerate fast after trauma, for example, hematopoietic bone marrow cells, the transitional epithelium in the urinary tract, the columnar epithelium in the intestinal tract, the squamous epithelium of skin, mouth, vagina, and cervix.

The second group are stable cells that usually remain in the $G_0$ stage (the resting phase) and have a low level of replication, but if the stimulation is present, they can return to the $G_1$ phase and proliferate. Examples of stabile cells are the epithelium of kidney tubules, the alveolar cells of the lung, the parenchyma of the pancreas, liver fibroblasts, smooth muscles, and endothelial cells.

Finally, permanent cells are not able to proliferate; and after the damage, they repair during the connective tissue proliferation. Examples of these cells are cardiac and skeletal muscles, and neurons.

The mechanism of scar formation can be divided into several steps: inflammation, cell proliferation, and remodeling. (Profyris, Tziotzios, and Do Vale 2012) The most crucial step is not to restore a tissue but to stop bleeding from the injured place. Coagulation starts exactly after trauma and finishes within hours. Collagen assists this process in the damaged area. Primary hemostasis is the formation of a plug at the injured place where endothelial cells become exposed. In the secondary hemostasis, there are two main pathways of blood clotting: the extrinsic and intrinsic pathways, and they come together in the common pathway. The extrinsic pathway is a primary stage in plasma mediated secondary hemostasis. Due to tissue damage, tissue factor (TF also known as platelet tissue factor or factor III) is released in the plasma, which results in binding of factor VIIa and calcium to boost the activation of factor X to Xa. The intrinsic pathway includes factors I (fibrinogen), II (prothrombin), IX (Christmas factor), X (Stuart-Prower factor), XI (Plasma thromboplastin), and XII (Hageman factor). (Robertson and Miller 2018)

In comparison with the extrinsic pathway, the intrinsic pathway is longer and more complex. The common pathway has descent steps from the activation of factor X to the formation of active thrombin which brakes fibrin into a cross-linked complex. In current concepts of coagulation, there are several steps. (Figure 1)

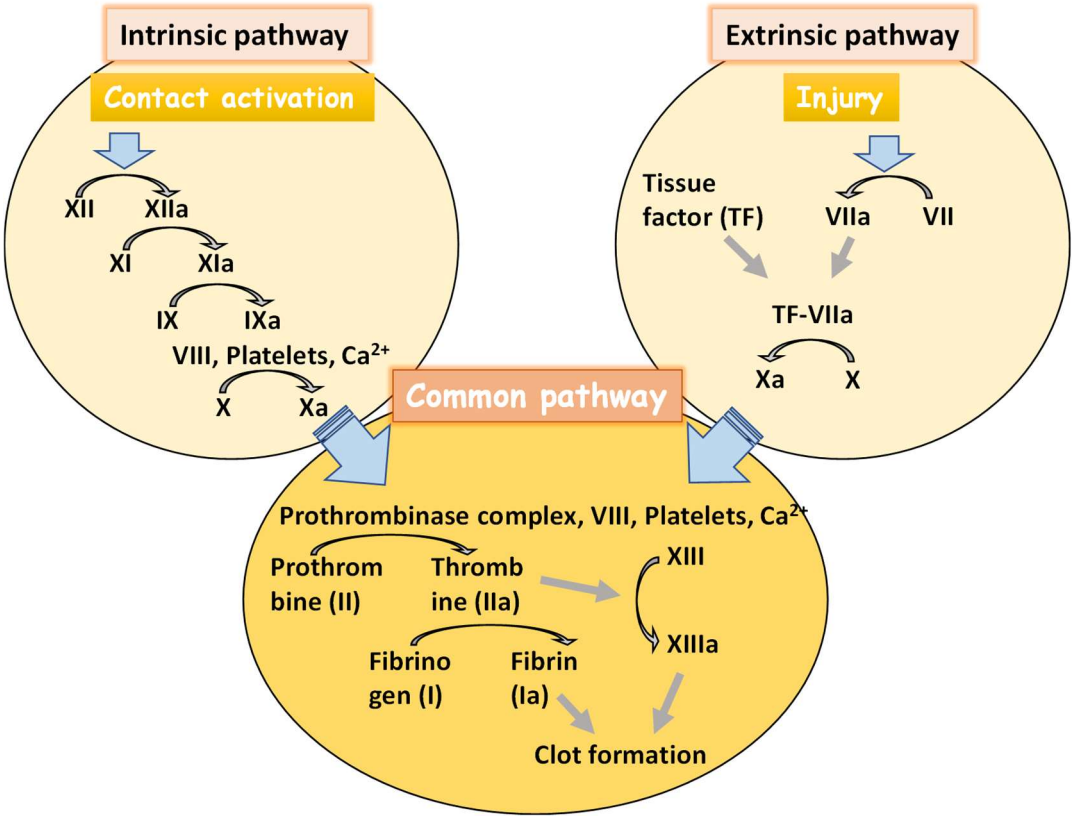



**Figure 1. A clot formation cascade**

There are three steps of the clotting (coagulation) cascade: the intrinsic pathway (factors XII, XI, IX, and VIII), the extrinsic pathway ( factor VII), and the common pathway. During clotting, cascade factor X may be activated by the extrinsic and intrinsic pathways. The common pathway has descent steps from the activation of factor X to the clot formation. Factors that are activated are shown with a lowercase "a".

The first step is an initiation which starts by the release of TF into the bloodstream and the formation of factor VIIa complex which leads to the activation of factor IX and X. Later on, factor Xa binds to factor II and forms thrombin (factor IIa). The next step is the amplification when thrombin that was created activates factor V to factor Va, factor VIII to factor VIIIa, then it activates factor XIa converting factor IX to factor IXa. Finally, platelets actively bind to factor Va, factor VIIIa and factor IXa. The propagation step is the activation of thrombin and platelets, thus leading to the activation of factor X which causes the formation of the prothrombin complex that converts prothrombin to thrombin. and furthermore, the activity of thrombin stimulates the conversion of fibrinogen to fibrin. The stabilization step involves the formation of thrombin that activates factor XIII (the fibrin stabilizing factor) by attaching fibrin polymers and contributes to fibrin stability and strength of a platelet plug. Also, thrombin stimulates thrombin-activatable fibrinolysis inhibitor (TAFI), the primary function of which is to defend clot against fibrinolysis. (Feng et al. 2019)(Grover and Mackman 2019)(Chaudhry and Babiker 2018)(Palta, Saroa, and Palta 2014)

## Inflammation

Tissue repair and regeneration also depend on the extent of injury and inflammation. When the injury is extensive in the presence of chronic inflammation, repair may predominate even when the damaged cells can regenerate.

The critical part of tissue regeneration and repair is the inflammatory response. Some of the immune cells are located in tissues, for instance, fibroblasts, macrophages, dendritic, and mast cells; others flow in the blood, for example, leukocytes, monocytes, and neutrophils that can detect cell injury or pathogen invasion. Their primary initiating factor of inflammation is intracellular or surface-expressed pattern recognition receptors (PRRs). Cells that are injured can release damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), and PRRs are capable of detecting them directly or indirectly.(Tang et al. 2012) When chronic inflammation is present, the cells responsible for the limitation of repair and tissue injury are enrolling to the place of infection or inflammation. Continuous DAMP release signals cause cellular stress.(Rosin and Okusa 2011) The combination of the adaptive and innate inflammatory cells on the one hand and the epithelial and stromal components on the other hand allows control of healing and fibrosis. In some cases, due to chronic inflammatory illnesses such as obesity, autoimmunity, atherosclerosis, chronic bacterial and viral infections, the DAMP release may occur. (Rubartelli and Lotze 2007) Firstly, the DAMP release leads to vasodilatation and tissue edema stimulated by mast cells. Secondly, DAMPS suppress the T and Natural Killer effector cells and support the Th2 response. At the same time, eosinophils encourage the elimination of injured cells and waste. Not only PAMPs and DAMPs are present in the extracellular environment and are responsible for the wound healing process, but in this activity, there are also other elements such as gaseous mediators (NO and CO), reduction-oxidation reaction (redox), hypoxia, low or high pH and the degraded matrix components. In normal circumstances, the inflammatory microenvironment quickly handles the damaged particles or pathogens. The essential factors of inflammation and fibrogenesis are summarized below (Table 2). (Newton and Dixit 2012) (Kendall and Feghali-Bostwick 2014)

**Table 2. Key mediators of inflammation and fibrogenesis**

| **Profibrotic factors acting on fibroblasts** | **Substance** | **Production site** | **Effects** |
|---|---|---|---|
| | TGFβ | White blood cells | Stimulation of resting monocytes and inhibition of activated macrophages. Stimulation of α-smooth muscle actin expression in pulmonary fibroblasts. Induction of NADPH oxidase 4 in fibroblasts. |
| | IL-1β | Fibroblasts | Inflammation promotion and fibrotic responses. |
| | IL-6 | T cells, skeletal muscle cells, macrophages | Stimulation of cellular differentiation, fibrosis, and inflammation. |
| | IL-13 | Mast cells, T lymphocytes | Stimulation of TGFβ production, proliferation of fibroblasts, collagen and MMP production. |
| | IL-33 | Smooth muscle cells and endothelial cells | Stimulation of fibrosis and inflammation. |
| | TNFα | Macrophages, T lymphocytes, NK cells, mast cells, eosinophils | Inflammation and fibrosis stimulation. |
| | FGF | | Fibrosis enhancement. |
| | PDGF | Platelets, smooth muscle cells, | Stimulation differentiation, proliferation, and ECM production. |

| | | | |
|---|---|---|---|
| | | endothelial cells and macrophages | |
| | Leukotrienes (LTB4, LTC4, LTD4, LTE4) | Leucocytes | Stimulation of fibroblasts proliferation and production of the matrix. |
| **Profibrotic factors released from fibroblasts** | VEGF | Fibroblasts | Angiogenesis promotion. |
| | IL-1 | Fibroblasts | Facilitation of inflammation and fibrosis. |
| | IL-6 | Fibroblasts | Facilitation of inflammation and fibrosis. |
| | IL-33 | Fibroblasts | Promotion of inflammation and fibrosis. |
| | Angiotensin II | Macrophages and myofibroblasts | Promotion of TGFβ mediated heart remodeling. Fibrosis enhancement. |
| | IGFII | Paracrine signals produced by fibroblasts | Stimulation of fibrotic response. |
| | IGFBP-3 | | Fibrosis enhancement. |
| | IGFBP-5 | | |
| **Autocrine factors** | TGFβ | Fibroblasts | Induction of malignancy transformation. Profibrotic action, promotion of proliferation, matrix production, formation of fibrosis, migration, and fibroblast and myofibroblast differentiation. |
| | IL-1β | Fibroblasts, macrophages | Pro-inflammatory interleukin, an induction of PDGF, and TGFβ production. |
| | IL-6 | Fibroblasts | Enhancement of inflammation and fibrosis formation. |
| | HGF | Fibroblasts | Wound repair, angiogenesis, and oncogenesis. |
| **Antifibrotic factors acting on fibroblasts** | $PGE_2$ | Almost all nucleated cells | Inhibition of fibroblast proliferation and suppression of collagen production. |
| | HGF | Fibroblast | Counteraction of fibrosis. |
| | PPAR ligands | Express in almost all tissues | Potent antifibrotic effects, reduction of β-catenin levels. |

**Cell proliferation**

Cell proliferation usually takes approximately ten days. There are several types of cells, such as epithelial cells, endothelial cells, and fibroblasts that participate in fibrogenesis.

Fibroblasts originate from the embryonic mesoderm tissues. They have well-developed rough endoplasmic reticulum and generate many variations of ECM proteins (collagen), ground substance, and adhesive proteins. Also, it plays a crucial role in ECM maintenance and reabsorption . Due to the chemotaxis feature, fibroblasts are able to migrate within tissue in response to chemical stimuli. In case of injury, they can cause contraction of the matrix that leads to the sealing of the open wound. Fibroblasts play an important role in fibrogenesis, for example, in the myofibroblast pathway of the TGF-β1 dependent differentiation. (Weiskirchen, Weiskirchen, and Tacke 2019)

Mesothelial cells originate from the embryonic mesoderm. Their main functions are the formation of layers that cover different cavities such as pericardial, peritoneal, and pleural and produce a lubricating fluid that helps the lungs glide smoothly at the time of breathing. The other function of these cells is the reabsorption of excessive fluid from the pleural cavity. Mesothelial cells play an essential role during trauma or infection. For instance, in pleural injuries, they assist in transporting white cells. Also, as a result of mesothelial-to-mesenchymal transition (MMT), these cells, might be genetically reprogrammed after the influence of specific stimuli. In a recent mouse model, the lineage analysis of stem cells demonstrated that MMT increased the proliferation of myofibroblasts and hepatic satellite cells during liver fibrogenesis, although this process might be stopped in vivo and in vitro by reversing the TGF-β pathway. (Tirado and Koss 2018)

Fibrocytes are of a mesenchymal origin and are phenotypically inactive due to a low amount of rough endoplasmic reticulum. These cells produce fibroblastic components such as collagen, fibronectin, and vimentin. When influenced by TGF-β, they can produce alpha-smooth muscle actin (α-SMA) which plays a role in angiogenesis and immunity. Fibrocytes can also migrate to the damaged area with blood flow. (de Oliveira and Wilson 2020)

Epithelial cells are located in different areas of the body, such as skin, urinary tract, blood vessels, and internal organs. Their primary role is absorption, protection and secretion. One of the critical features is the ability to differentiate into different types of cells. During epithelial-to-mesenchymal transition (EMT), epithelial cells become transited cells that become sensitive to the fibroblast's specific protein (FSP1). The plasticity of epithelial cells allows them to become a source of myofibroblasts in the damaged cells. (Kevin Range 2012)

Endothelial cells are mainly responsible for the formation of a barrier in the endothelium of capillaries, venules, vein, arterioles, and arteries. Being stimulated by TGF-β, endothelial cells can release α-SMA and become able to convert into mesenchymal cells (endothelial-to-mesenchymal-transition, EndoMT). It was demonstrated that EndoMT could lead to fibrosis in the organs such as heart, kidney, and lungs. (Öztekin Long, Nicole, M and Badre 2008)

Pericytes are fibroblast-like cells that surround endothelial cells in blood vessels. Pericytes are able to contract and consequently control blood flow. In the case study, it was suggested that this type of cells produce α–SMA, neural/glial antigen (NG2) and platelet-derived growth factor receptor-β (PDGFR-β). Moreover, they are a source of myofibroblasts in pulmonary tissues. Another study reported that Foxd1 progenitor-derived pericytes prominently lead to the lung fibrosis. Öztekin Long, Nicole, M, and Badre.

Vascular smooth muscle cells are responsible for the relaxation and contraction of blood vessels. As a result of the injury, they produce α–SMA, vimentin, desmin, and other compounds. It has also been shown that collagen type I is induced by bradykinin secretion in vascular smooth muscle cells through the TGF-β1 activation.(Z. Liu et al. 2017)

There are two main processes involved in the process of repair: the formation of granulation tissues and wound contraction. Wound contraction usually starts on day 2-3 and is finished within two weeks. The primary cells that are responsible for this process are myofibroblasts, the unique cells that have features of fibroblasts and smooth muscle. The main role of these cells is the contraction of the wound by up to 80%. Granulation tissue is soft in touch and has a pink color. Granulation is a sign of tissue repair; it is formed by three steps: the inflammatory phase, the clearance phase, and the ingrowth of granulation tissue. During the inflammation phase, cells that are predominantly involved in the process are monocytes and neutrophils. The clearance phase is characterized by the release of autolytic enzymes from dying cells as well as enzymes from neutrophils; macrophages also clear necrotic debris. The final phase is the ingrowth of granulation tissue during which granulation tissue is formed. This phase can be divided into two processes: angiogenesis and fibrogenesis. (Baum and Duffy

2011)(Bochaton-Piallat, Gabbiani, and Hinz 2016)(Alhajj, Bansal, and Goyal 2020)

Angiogenesis (neovascularization) is the development of blood vessels. Angiogenesis could be the result of sprouting either from pre-existing blood vessels or from stem cells. There are a few steps in the angiogenesis from pre-existing blood vessels. The first one involves vessel dilatation that is mediated by NO, and the second step includes an increased vascular permeability that is mediated by the vascular endothelial growth factor (VEGF). The next step is a breakdown of the basement membrane and the formation of a vessel sprout. The other step is the migration of endothelial cells toward chemotactic and angiogenic stimuli that cause a proliferation of endothelial cells and their maturation leading to capillary tube remodeling. The final phase of angiogenesis is the accumulation of periendothelial cells (pericyte). (Papetti and Herman 2002)

Angiogenesis from stem cells develops from endothelial precursor cells (EPC) stored in the bone marrow, and if needed, they migrate to the place of injury. (Aldair and Montani 2010)

**Fibrogenesis**

During angiogenesis, new blood vessels are formed. Fibroblasts derived from the mitosis process in pre-existing fibroblasts or from fibrocytes are also present around new blood vessels.

Remodeling (maturation phase) after injury usually takes place from several weeks to months or years and depends on what type of tissue is damaged, injury location, and the associated comorbidities (infections, arteriosclerosis, vein thrombosis, nutritional status, diabetes, and some drugs). Remodeling includes three steps: functional recovery, wound contraction and an increasing tensile strength of the wound. (Cañedo-Dorantes and Cañedo-Ayala 2019) The maturation phase is characterized by the formation of scar tissue as well as by the absence of inflammatory cells (neutrophils, macrophages) and the termination of blood vessel proliferation. Granulation tissue in the scar is replaced by dense collagen. The scar initially consists of a provisional matrix that contains fibrin, fibronectin, and collagen type III, but later on, collagen type III is replaced by collagen type I. (Reinke and Sorg 2012) The next step is wound contraction, with the main goal being a reduction of a gap between two cut margins. Myofibroblasts play a key role during this phase. Collagen type I is responsible for the last step – an increase in the strength of the wound. The recovery of ~80 % of the original tissue strength will usually take up to three months.

Skin wound healing can be subdivided into primary and secondary unions. (Alhajj, Bansal, and Goyal 2020) By primary union (first intention), regeneration occurs with a minimum scaring tissue, for example, a clean surgical wound. By secondary union (secondary intention), the wound has the larger tissue defects with a wide distance between edges; wound healing by secondary intention occurs by regeneration and scarring. In some cases, due to abnormal wound healing, keloids or hypertrophic scars might occur. In a hypertrophic scar, there is a build-up of extra collagen fibers, which results in the elevation of the scar. Fibrillar collagen fibers are located parallel to the epidermis with a lumpy red scar, and they do not extend beyond the original scarring area. Usually, hypertrophic scars affect younger individuals with the delayed healing of wounds caused by underlying conditions such as infections, and usually, there is an improvement with the treatment. Morphologically keloids are characterized as eosinophilic, focally fragmented complexes of haphazardly arranged collagen. Also, in comparison with hypertrophic scars, one-third of keloids have α–SMA- expressing myofibroblasts. The scar tissue in keloids grows beyond the inflammation area, and it is difficult to treat. (Moshref et al. 2010)

**Physiological injury healing vs. pathological fibrosis**

Fibrosis of the organ tissues is caused by parenchymal cell destruction; as a result of tissue trauma, macrophages become active and enter the damaged area. Also, local immune cells create chemokines

and cytokines which activate mesenchymal cells located close to the injury area. The next step is the initiation of the production of extracellular matrix (ECM) and the elevated manufacturing of pro-inflammatory cytokines and angiogenic factors. (Weiskirchen, Weiskirchen, and Tacke 2019) After trauma, cells produce inflammatory mediators that provoke the anti-fibrinolytic coagulation cascade, the first step of which is the coagulation. During this stage, platelets are activated and form fibrin clots. Next, platelets liberate inflammatory chemokines. Then the infiltration of leukocytes happens into the injured site, and they excrete profibrotic cytokines (TGF-β and IL-13). This process is called the inflammation stage. Neutrophils are typically engaged in the infiltration process earlier than lymphocytes and macrophages. (Rosales 2018) The main role of leucocytes is to remove any microorganisms and/or the contaminated material from the wound.

The proliferation stage follows the inflammation stage; during this stage, fibroblasts become active, and myofibroblasts induce and deposit ECM that will be a framework through the tissue regeneration action. The last step is remodeling. (Gonzalez et al. 2016) In physiological recovery, the extra volume of ECM is degraded, myofibroblasts and fibroblasts go through apoptosis, and inflammatory cells leave the recovered tissues. On the other hand, the fibrosis process extends inflammation, and myofibroblasts stimulate the elevated accumulation of ECM which leads to the creation of a perpetual fibrotic scar. The contrasting features that distinguish fibrosis from normal wound healing are chronic inflammation, the persistence of myofibroblast activity, MMP-TIMP imbalance, and the excessive ECM deposition. These differences are very important to be understood from the therapeutic point of view because drugs can be prescribed to target these particular molecular disturbances.

Fibroblasts control synthesis and catabolism of collagen as well as an increase in collagen amount by MMPs and their inhibitors (tissue inhibitors of TIMPs). Changing the balance between these mechanisms will cause the elevation or dropping of collagen amount inside the injured area. In addition, an increasing number of mesenchymal cells will aggravate response. During the remodeling phase, fibroblasts synthesize collagen at a higher rate than they degrade it, leading to the continuous accumulation of collagen. Generally, inflammation stimulates fibrosis. According to some reports, fibrosis is not always driven by inflammation. This fact clarifies the shortage of efficacy of anti-inflammatory mediators in the management of the fibrotic disease. (Kryczka and Boncela 2015)(Wynn 2007)

**Fibrosis prevention and treatment options**

Prevention strategies for the development of fibrosis are very important in the modern world because life expectancy and the patients' quality of life are expected to rise gradually. When patients are aware of avoidable risk factors for this condition, they, for example, should quit smoking to prevent the development of pulmonary fibrosis and should treat all acute diseases in time to prevent the development of chronic conditions. Concerning the unavoidable factors such as genetics, the existing comorbidities (diabetes mellitus, herpes virus infection), the environmental exposures, air pollution, the use of some medicine, people should pay extra attention to their health state and in case of any changes, they should seek medical advice. (Zaman and Lee 2018)

Anti-inflammatory drugs are widely used to manage fibrosis due to a strong connection between inflammation and fibrosis.(Suthahar et al. 2017)(Simon et al. 2019)(Lands and Stanojevic 2019) As a result of better understanding of the pathology of fibrosis, molecular targets of this condition and modern drugs affecting it have been recently discovered. A single-component medication is characterized by the presence of a single component that can target either extracellular or intracellular factors. The main extracellular targets are MMPs, growth factors, TNF. Most of the drugs targeting intracellular factors are small molecules; they can easily translocate inside the cytoplasm compared

with other large molecules like monoclonal antibodies which experience more problems in crossing the cell membrane.

There are four categories of intracellular factors: nuclear receptors, enzymes, other proteins, and epigenetics. (Li et al. 2017) The antifibrotic medication suppresses kinases located in the cytoplasm, and moreover, it inhibits the translocation of transcription factors responsible for the expression of profibrotic genes. Epigenetic regulators represent a very specific category of fibrotic treatment. The main target of epigenetic-based management is microRNA (miRNA). Anti-miRs - are microRNA oligonucleotides that are able to neutralize miRNAs when deposited inside the cell. There are 1400 miRNAs found in humans. They are mainly located in extrons, introns, and the untranslated regions of protein-coding genes. MiRNAs like let-7, miR-21, miR-29, miR-155 play an important role in fibrosis, particularly in TGF-β control. Let-7 and miR-29 are antifibrotic; in contrast, miR-21 and miR-155 are profibrotic, and their expression will rise during the fibrotic reaction. On the other hand, the decreased expression of miR-29 in systemic sclerosis (SSc) fibroblasts lead to the increased levels of type I and III collagen. The reduction of miR-29 was noted in the fibrotic reaction in the lungs, heart, and kidneys. IL-4, TGF-β, and PDGF-B reduced the level of miR-29 in SSc fibroblasts as well as in the bleomycin-induced model of skin fibrosis. (Maurer et al. 2010)(Harmanci et al. 2017). According to another study, miR-21 was highly elevated in animal and human models of transplant kidney nephropathy. MiR-21$^{-/-}$ mice experienced less interstitial fibrosis in response to kidney injury that was pheno-copied in wild-type mice that were treated with anti-miR-21 oligonucleotides. The peroxisome proliferator-activated receptors (Pparα) and Mpv171 are two main metabolic pathways that are key targets for miR-21. Also, miR-21 down-regulated inhibitors of angiogenesis and migration, especially the RECK (the reversion-inducing cysteine-rich protein with Kazal motifs) and the atypical matrix metalloproteinase (MMP) inhibitor that led to the enhanced MMP activity in kidney injury. As a result of the administration of oligonucleotides that silenced miR-21, a reversal of the deleterious action of miR-21 in kidney injury was noted. Some studies demonstrated a significant effect of miR-21 on pulmonary and cardiac fibrosis.(Chau et al. 2013)

In multi-component therapy, there are more than single elements. The main approach of this treatment is using numerous ingredients that act on numerous targets. In fibrosis, there are multiple pathological pathways and multi-component drugs that are able to modulate these pathways and create synergistic effects. In the table below, single and multi-component medications used nowadays in the treatment of fibrosis are summarized (Table 3). (Li et al. 2017)

**Table 3. Single- and multi-component medications targeting fibrosis factors**

| **Single-component medications targeting extracellular factors** | | | | |
|---|---|---|---|---|
| **Group** | **Target or mechanism type** | **Mechanism of action** | **Drug name** | **Disease** |
| Growth factor | Extracellular TGF-β signaling | TGF-β, inhibitor | Pirfenidone | IPF |

| | | | | |
|---|---|---|---|---|
| | PDGF/VEGF | PDGFR, antagonist | Imatinib | SSc, Nephrogenic systemic fibrosis, IPF |
| | | VEGFR/PDGFR, antagonist | Nintedanib | Scleroderma, IPF |
| | TNF | TNF, inhibitor | Talidomide | IPF |
| | | TNF, inhibitor | Etanercept | IPF |
| | | TNF, inhibitor | Belimumab | SSc |
| Cytokines | Interleukin | IL-1R1, antagonist | Anakinra | Cystic fibrosis |
| | | IL-1 βR, antagonist | Rilonacept | SSc |
| | Interferon | IFN-γR, stimulant | Actimmune | IPF, Cystic fibrosis, Liver fibrosis |
| MMP/TIMP | MMP/TIMP | MMP/TIMP, inhibitor | Marimastat | Liver fibrosis |
| Other proteins and peptides | Endothelin | ET-1 receptor, antagonist | Macitentan | IPF |
| | | | Bosentan | IPF |
| | | | Ambrisentan | IPF, SSc |
| | Angiotensin II | AT1 receptor, antagonist | Losartan | Cystic fibrosis, Liver fibrosis |
| | GPCR | Prostacyclin receptor, agonist | Iloprost | SSc |
| | | | Treprostinil | IPF, SSc |
| **Single-component medications targeting intracellular factors** | | | | |
| Enzymes | mTOR | mTORC1/2, inhibitor | Rapamycin (Sirolimus) | Renal interstinal fibrosis |
| | JAK-STAT | JAK1/JAK2, inhibitor | Ruxolitinib | Myelofibrosis |
| | PI3K-Akt | Akt, inhibitor | Omipalisib | IPF |
| | MAPK | MAPK, inhibitor | MMI-0100 | IPF, Cardiac fibrosis |
| | NF-kB | IKK, inhibitor | IMD-1041 | Cardiac fibrosis |
| Nuclear receptors | PPAR | PPAR-γ, agonist | Rosiglitazone | Liver fibrosis |
| Other proteins | Intracellular TGF-β signaling | SMAD2/3, inhibitor | Pirfenidone | IPF, SSc |
| | | SMAD3/4, inhibitor | Pentoxifylline | Skin fibrosis |

| | | | | |
|---|---|---|---|---|
| | | SMAD3, inhibitor | SiS-3 Glycyrrhizin | Renal fibrosis, Liver fibrosis |
| Epigenetics | miRNA | miR-21, inhibitor | Anti-miR-21 | Renal fibrosis, IPF |
| **Multi-component drugs** | | | | |
| | TGF-pc/MMP-2c | | Fuzhenghuayu capsule (FZHY) | Liver fibrosis |
| | TNF-α/TGF-β | | Danggui-Buxue-Tang (DBTG) | IPF |

TGF- β, transforming growth factor- β; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; TNF, tumor necrosis factor; IFN-γR, interferon –γ receptor; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase; ET-1 receptor, endothelin-1 receptor; AT1 receptor, angiotensin II receptor type 1; GPCR, G protein-coupled receptor; mTOR, mechanistic target of rapamycin; mTORC1, mechanistic target of rapamycin complex 1; JAK-STAT, janus kinase/signal transducers and activators of transcriptions; PI3K-Akt, phosphoinositide 3-kinase/protein kinase B; MAPK, mitogen-activated protein kinase; NF-kB, nuclear factor kappa-light –chain- enhancer of activated B cells; IKK, I-kappa B kinase; SMAD3, mothers against decapentaplegic homolog 3.

Only nintedanib and pirfenidone have been approved by FDA for the treatment of fibrosis, particularly of idiopathic pulmonary fibrosis (IPF), and ruxolitinib has been approved by FDA for the treatment of myelofibrosis; other medications are still experimental, and some of them are under ongoing clinical trials the results of which might help improve the understanding of the fibrosis pathway. Nintedanib medication is a small molecule kinase inhibitor that reduces the proliferation and migration of lung fibroblasts. Nintedanib inhibits receptor tyrosine kinases (RTKs), for instance, FGFR1-3, VEGFR1-3, Fns-Like tyrosine kinase-3 (FLT3), PDGFR α and β. Also, this drug inhibits kinase signaling pathways. It's main side effects are nausea, diarrhea, and liver dysfunction. (Valenzuela et al. 2020),(Wind et al. 2019) Pirfenidone treatment mainly reduces fibroblast proliferation and causes the inhibition of collagen synthesis and down-regulation of profibrotic cytokines. As a result of inhibition, it causes the suppression of TGF-β2 mRNA levels and TGF-β2 protein and the suppressed expression of the TGF-β pro-protein convertase furin. Although, this drug decreases the MMP-11 protein levels. Pirfenidone has some severe side effects such as photosensitivity, nausea, rash, stomach pain, upper respiratory tract infections, diarrhea, fatigue, headache, indigestion, dizziness, vomiting, decreased or loss of appetite and gastroesophageal reflux disease that may lead to medication intolerance and discontinuation. (Margaritopoulos, Vasarmidi, and Antoniou 2016),(Hughes et al. 2016),(Moran-Mendoza et al. 2019). Ruxolitinib is widely used in myelofibrosis treatment. This drug is a kinase inhibitor that is selective for JAK1 and 2. The main role of these kinases is affecting growth factor signaling and cytokine release. The known side effects of this medicine are anemia, thrombocytopenia, increased liver enzymes, and diarrhea.(Elli et al. 2019) However, many physicians

and scientists are still facing numerous challenges in treatment of patients with fibrosis. In clinical practice, a long-term use of nintedanib is still discussed. Research in this area will help improve patient outcomes.(Valenzuela et al. 2020)

**The role of cannabinoids and cannabis in inflammation and fibrosis**

Recently, the endocannabinoid system (ECS) has received a significant attention from mainstream medical professionals, being viewed as an important therapeutic target for many pathological conditions. Human physiology significantly depends on a proper function of this system. The ECS has been established as an important homeostatic regulator. It affects almost all functions of the body. It consists of endocannabinoids (2-AG, AEA), their metabolic enzymes and receptors, including cannabinoid receptors 1 (CB1), cannabinoid 2 (CB2), transient receptor potential channels of the vanilloid subtype 1 and 2 (TRPV1, TRPV2), G protein-coupled receptors 18, 55,119 (GPR18, GPR55, GPR119).(Laezza et al. 2020)

The imbalance in the functioning of ECS can significantly impact the proper functioning of the whole organism, including fibrosis and inflammation processes. For example, the activation of the CB1 receptor leads to fibrogenesis, while the enhancement of the CB2 receptor inhibits fibrosis progression.(Mallat et al. 2011) In animal models, it was demonstrated that the deletion of CB1 caused an improvement of liver fibrosis, whereas CB2 deletion resulted in an elevated amount of collagen accumulation and an increased inflammation.(Patsenker and Stickel 2016) Concerning inflammation, the use of CB2 receptor agonists was documented to inhibit the infiltration of inflammatory cells into liver tissue. In addition, CB2 receptor knockout mice had the more profound inflammation and damage to the liver than wild-type mice.(Vaccarino 2008)

Various positive impacts of cannabis on humans were reported since the antic period. Cannabis is widely known as a plant with psychoactive properties. It includes over 500 compounds such as different cannabinoids, terpenoids, fatty acids, and flavonoids. Cannabinoids (known as phytocannabinoids in contrast to endocannabinoids) act via the endocannabinoid system. The most abundant are cannabidiol (CBD) and Δ9 -tetrahydrocannabinol (Δ9 -THC); they are the most studied cannabinoids with numerous documented medicinal properties.(Zurier and Burstein 2016)(Lafaye et al. 2017). Although, it was reported that the effect of cannabis extracts was much more potent in comparison with its isolated compounds. This is known as an entourage effect. Terpenoids and minor cannabinoids significantly contribute to this process. Looking at the enormous varieties of cannabis cultivars nowadays, it is clear that research in this field should continue to discover new possibilities of fibrosis treatment.(Russo 2019)

According to previous reports, some of the cannabinoids can be used as anti-inflammatory agents. Currently in medical practice, these substances have documented little negative impact on patients in comparison with other drugs. Cannabinoids have other mechanisms of action on inflammation in comparison with nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs inhibit the activity of cyclooxygenase enzymes, prostaglandins.(Zurier and Burstein 2016) Recently it has been discovered that cannabinoid receptor signaling regulates the proliferation and function of fibroblasts which are crucial cells in scar formation. (Vaccarino 2008) Cannabis/cannabinoids have been proven to have the potent anti-inflammatory properties. By suppressing inflammation, they may stop the progression of repair by scarring. It has been shown that cannabinoids and cannabis extracts suppress the pro-inflammatory cytokines Il-2, IL-1β, TNF-α, IFN-γ, IL-12, IL-8, IL-6, IL-15 in different cell lines and animal models. Due to this, the inflammatory process will be prominently inhibited. (Vaccarino 2008)

A lot of research has already been done, and currently many studies are undergoing on the use of endo-, synthetic, and phytocannabinoids in the fibrosis field. In one in vivo study where a mouse model of type I cardiomyopathy was used, it was demonstrated that CBD treatment diminished the

diabetes-associated cardiac fibrosis. A significant decrease of collagen deposition and the expression of profibrotic genes like MMP-2, MMP-9, TGF-β, connective tissue growth factor, fibronectin, collagen-1 were noted.(Montecucco and Marzo 2012)

Liver fibrosis is a usual complication of many long-lasting liver illnesses such as viral hepatitis B and C, non-alcoholic steatohepatitis, drug-induced liver injury, alcohol abuse, and autoimmune conditions. In long-lasting liver damage, the activated hepatic stellate cells (HSCs) and myofibroblasts are the main contributors to the development of liver cirrhosis and hepatocellular cancer.(R. Fu et al. 2011) An in vitro study performed on hepatic stellate cells (HSCs) documented that CBD induced the programmed cell death of these cells. (Lim, Devi, and Rozenfeld 2011) This effect was independent of cannabinoid receptors and was the result of endoplasmic reticulum stress induction. In addition, CBD enhanced the pro-apoptotic pathway IRE1/ASK1/c-Jun N-terminal kinase, which resulted in HSCs death. This CBD-induced programmed cell death of activated HSCs was confirmed in vitro in human, mouse and rat cell lines, but not in the quiescent cell lines. The well-known fact that the activated HSCs play a crucial role in the development and continuation of liver fibrosis supports the fact that cannabis extracts might be turned into promising antifibrotic drugs as they lead to the selective apoptosis of activated HSCs. The results of this study are very encouraging for further investigation of CBD in vivo. (Lim, Devi, and Rozenfeld 2011) In addition, a meta-analysis of nine studies performed on 5,976,026 patients concluded that marijuana did not elevate the prevalence or progression of liver fibrosis in patients with hepatitis C or hepatitis C HIV co-infection. (Farooqui et al. 2019) Also, it was noted that marijuana users had a reduced prevalence of non-alcoholic fatty liver disease (NAFLD). Furthermore, these patients consumed more sodas and alcohol, therefore the healthy lifestyle was not a cause of the reduced prevalence of NAFLD. This effect might be induced by reducing fat depositions via omega-3 fatty acids and the impact of CBD on insulin sensitivity.(Farooqui et al. 2019)

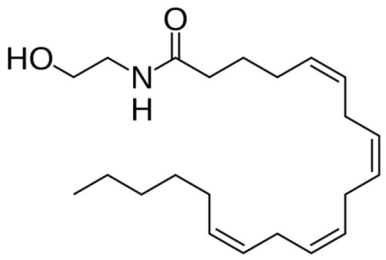
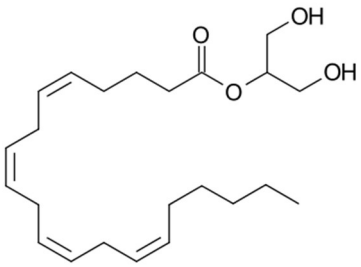
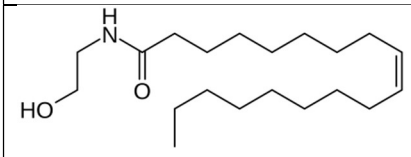
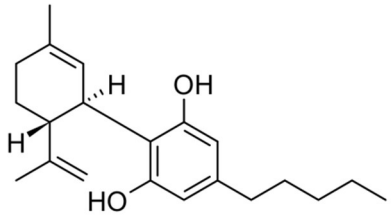
Concerning the effect of THC, it has been shown that it inhibits the proliferation of liver myofibroblasts and stellate cells via CB2 receptors and leads to their programmed cell death. Due to this, THC may also possess antifibrotic properties.(Tam et al. 2011)

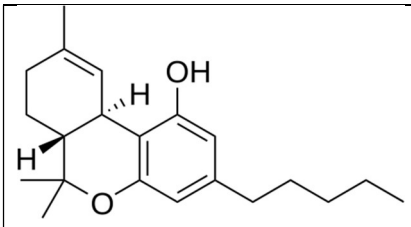
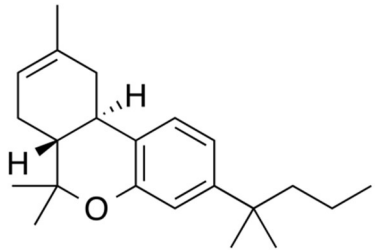
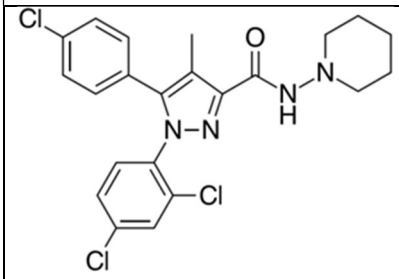
The endocannabinoid, AEA, demonstrated the anti-fibrogenic features by suppressing the proliferation of HSC and necrosis induction. The elevated AEA levels were documented in cirrhotic patients, which might be a response to fibrosis. This endogenous cannabinoid can trigger the topical inflammatory response and systemic dilatation of vessels, therefore the opportunity for fibrosis treatment was restricted.("Role of Cannabinoids in Chronic Liver Diseases" n.d.) Another endocannabinoid, 2-AG, was considered as a fibrogenic agent. When used in higher doses in vitro on HSC, it activated fibrosis via the membrane cholesterol-dependent mechanism.(Liggett 2014) Another endogenous cannabinoid, oleoylethanolamide (OEA), was used in a mouse model of hepatic fibrosis and showed the inhibition of collagen deposition and suppression of collagen type I and III gene expression, α-SMA, MMP2, MMP9, and TIMP1. These effects were mediated through the PPARα mechanisms.(McVicker and Bennett 2017)

The next group of cannabinoids, synthetic cannabinoids, was also shown to be beneficial for fibrosis treatment. An in vitro study performed on pulmonary fibroblasts demonstrated that JWH133, a CB2 receptor agonist, suppressed the collagen type I and α-SMA and inhibited the proliferation and migration of fibroblasts. These effects were reversed by the use of a CB2 receptor antagonist, SR144528. In vivo studies on bleomycin-induced lung fibrosis in mice, showed that JWH133 decreased the lung density, and the fibrotic score and histological results illustrated the suppression of the collagen accumulation and inflammatory response. In both models, this particular synthetic cannabinoid inhibited the crucial pathway of fibrogenesis, TGF-β1/Smad2.(Q. Fu et al. 2017). WIN-55,212, a nonselective CB1 and CB2 agonist as well as JWH133 were assessed on the mouse model of systemic sclerosis. They prevented the development of dermal and pulmonary fibrosis and inhibited

the proliferation of fibroblasts. $CB2^{-/-}$ mice developed a significantly enhanced skin and lung fibrosis compared with $CB2^{+/+}$ mice. In this study, the significant influence of the CB2 receptor on fibrosis development was demonstrated.(Servettaz et al. 2010) Rimonabant, a CB1 receptor antagonist, was assessed on rat models of liver cirrhosis induced by carbon tetrachloride. Fibrosis was prominently suppressed by the use of this synthetic cannabinoid in rats compared with rats in the vehicle group. Rimonabant restricted the fibrogenic (TIMP-1, TGF-β, MMP13, MMP2, MMP9, MMP1, MMP8) inflammatory mediator (TNF-α, MCP-1) gene expression. In addition, Rimonabant treatment induced a prominent increase in the expression of the CB2 receptor. (Giannone et al. 2012) Table 4 summarizes type of cannabinoids and their mechanism of action (Table 4)

**Table 4.**

| Compound | The mechanism of action |
|---|---|
| **Endocannabinoids** | |
|  AEA | Suppressing the proliferation of HSCs and induces their necrosis |
|  2-AG | Generally considered as a fibrogenic agent, however it is able to suppress fibrosis via the membrane cholesterol-dependent mechanism. |
|  OEA | The inhibition of collagen deposition and suppression of collagen type I and III gene expression, α-SMA, MMP2, MMP9, and TIMP1. These effects were mediated through the PPARα mechanisms. |
| **Phytocannabinoids** | |
|  CBD | The apoptosis induction of HSCs as result of the induction of endoplasmic reticulum stress and the enhancement of the pro-apoptotic pathway IRE1/ASK1/c-Jun N-terminal kinase. |

| | |
|---|---|
|  THC | The inhibition of miofibroblast proliferation and stellate cells, the induction of their apoptosis via CB2 receptors. |
| **Synthetic cannabinoids** | |
|  JWH-133 | The suppression of collagen type I and α-SMA, inhibition of fibroblast proliferation and migration. The down-regulation of the TGF-β1/Smad2 pathway. |
|  Rimonabant | The suppression of gene expression of fibrogenic mediators (TIMP-1, TGF-β, MMP13, MMP2, MMP9, MMP1, MMP8, TNF-α, MCP-1) |

**Cannabis and cannabinoids may replace the known therapies for fibrosis**

Due to the lack of effective therapies for fibrosis, new more effective and modern therapies with less side effects need to be developed. The currently used drugs suppress the fibrogenetic pathways and reduce the progression of fibrosis. Similarly, cannabis extracts can also affect key profibrotic factors and pathways. Cannabinoid signaling regulates the proliferation and function of fibroblasts which are crucial cells in scar formation. The active suppression of fibroblast proliferation leads to the inhibition of collagen formation and deposition. As previously explained, cannabinoids can actively suppress inflammation by downregulating the pro-inflammatory cytokines such as Il-2, IL-1β, TNF-α, IFN-γ, IL-12, IL-8, IL-6, IL-15. Due to this effect of cannabis, the fibrosis progression may stop. In comparison with drugs currently applied for treating pulmonary fibrosis patients, cannabinoids can also suppress the MMP/TIMP, PPAR mechanisms and other pathways involved in fibrogenesis (Table 5). We can conclude that cannabis affects the same pathways as the currently used medicine in fibrosis treatment, but it has the little- documented negative effects on patients.

**Table 5. A comparison of target molecules in treatment of fibrosis using modern therapy vs cannabis treatment**

| **The mechanism of action of asingle-component medication vs cannabis** | |
|---|---|
| **A single-component medication:** | **Cannabis** |
| • TGF-β inhibitor<br>• PDGFR antagonist<br>• TNF inhibitor<br>• IL-1 antagonist<br>• IFN-γ stimulant<br>• MMP/TIMP inhibitor<br>• mTOR inhibitor<br>• JAK-STAT inhibitor<br>• PI3K-Akt inhibitor<br>• MAPK inhibitor<br>• NF-kB inhibitor<br>• miR-21 inhibitor | • TGF-β inhibitor<br>• TNF inhibitor<br>• MMP/TIMP inhibitor |
| **The mechanism of action of a multi-component medication vs cannabis** | |
| **A multi-component medication:** | **Cannabis** |
| • TGF-pc/MMP-2c inhibitor<br>• TNF-α/TGF-β inhibitor | • TGF-β1/Smad2 inhibitor |

## Conclusion

Fibrosis is a pathological process that may affect many organs; and aging is a great risk factor for the diseases' progression. (Hecker et al. 2015) A significant improvement in understanding the tissue fibrosis pathways may give us a chance in the future to discover an effective antifibrotic treatment. Many studies have been performed to understand the molecular mechanisms, the cellular basis, and the most prominent characteristics of fibrosis in human organs. In most tissues and organs, the fibrosis mechanisms are similar, but the regeneration and regression processes are different across organs and tissues. Mainly this diversity is due to the difference in the regenerative capacity of each tissue or organ. (Friedman 2015)

Based on reports presented in this review, we can summarize that cannabis extracts can positively interact with the key profibrotic factors and pathways. In comparison with modern antifibrotic medications, cannabinoids have fewer negative effects on patient's health.

Endocannabinoid system modulation is a modern approach for the treatment of different fibrotic conditions. This aspect of treatment has not been sufficiently studied. A more detailed research should be done to find a patient-oriented treatment and improve patients' quality of life. It would be very encouraging to find the curative option for this devastating condition that will help millions of patients worldwide with minimal side effects.

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