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Investigating the therapeutic potential of low-level laser therapy in mitigating liver fibrosis

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Abstract

Liver fibrosis is a significant global health issue characterized by the progressive accumulation of extracellular matrix (ECM), leading to hepatocyte dysfunction and disruption of liver architecture. This condition arises from hepatocyte injury and inflammatory cell infiltration, triggering the trans differentiation of hepatic stellate cells (HSCs) into myofibroblasts that produce collagen, contributing to fibrosis. A key factor in this pathology is the excessive production of reactive oxygen species (ROS) due to various insults such as toxic exposure or viral infection, which further exacerbate hepatocyte damage and fibrogenesis. The activation of nuclear factor-kappa B (NF-κB) amplifies the inflammatory response. Therapeutic interventions targeting oxidative stress and inflammation, such as the nuclear factor erythroid 2-related factor 2 (Nrf2) and peroxisome

proliferator-activated receptor gamma (PPARγ) pathways, have shown promise in mitigating fibrosis by enhancing antioxidant defenses and regulating inflammatory processes. Additionally, photobiomodulation therapy (PBMT), particularly low-level laser therapy (LLLT), has emerged as a potential non-invasive approach to reduce oxidative stress and inflammation. However, the specific mechanisms by which LLLT affects liver fibrogenesis require further investigation. This review aims to explore the potential of Low-Level Laser Therapy (LLLT) in mitigating liver fibrosis by examining its impact on the activation of antioxidants and anti-inflammatory cytokines. It focuses on elucidating how LLLT may stimulate molecular pathways, including Nrf2 and PPARγ, which are crucial regulators in the fibrogenesis process.

Keywords: Low-level laser therapy; Liver fibrosis; Oxidative stress; Inflammation; Nuclear factor erythroid 2-related factor 2 (Nrf2); Peroxisome proliferator-activated.

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1. Introduction

Liver fibrosis is a worldwide health issue that causes considerable morbidity and mortality (Friedman, 2003) it is caused by long-term liver damage. It is identified as a chronic wound-healing response to various stresses. It has been identified as a complex chronic process involving excessive deposition of extracellular matrix (ECM) proteins (glycoproteins, collagens, and proteoglycans) and hepatic stellate cell (HSC) activation (Friedman, 2000; Pan et al., 2020). Liver fibrosis is the common histopathologic feature that has the greatest impact on mortality. Liver cirrhosis develops gradually and is followed by secondary issues such as

hepatocellular carcinoma (HCC) and liver failure, leaving only liver transplantation as the treatment option (Berumen et al., 2021).

In population-based cohorts in Europe, the detection rates of hepatic fibrosis ranged from 0.7% to 7.5%. Nonalcoholic fatty liver disease (NAFLD)has been considered the most common cause of liver fibrosis in all studies (Harris et al., 2017). Based on the evaluation technique and demographics, estimates of advanced fibrosis. prevalence in North America has ranged from 3.2% to 10.3%. In Asia, few studies have been conducted to establish the incidence of liver fibrosis in both the general population and risk populations, while Hong Kong studies found elevated levels of advanced fibrosis in 2% and 17.7% of these two groups, respectively. Which 2 groups in Africa or Latin America, liver fibrosis is responsible for mortality due to hepatitis B(HBV) and (HCV) infections (Gines et al., 2022).

Hepatotoxic and cholestatic injuries are the primary etiologies of liver fibrosis. Hepatotoxic damage is caused by cellular injury caused by external causes such as viral infections (HBV and HCV), and alcoholic and non-alcoholic steatohepatitis (Roehlen et al., 2020). While cholestatic damage is defined as decreasing or blocking the bile flow, this occurs due to several illnesses including primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and biliary atresia(Sharma & Nagalli, 2021). A liver biopsy is the gold standard for the diagnosis and staging of liver fibrosis. There are numerous classification systems for liver fibrosis, including The Knodell score, The preferred Batts-Ludwig and Scheuer classification of fibrosis, and the Ishak scale. The Knodell score, developed in 1981, distinguishes three phases of fibrosis; 1) Zero fibrosis (no fibrosis as well as fibrous portal enlargement), 2) Bridging fibrosis (periportal fibrosis) (portal–portal or portal–central linkage), and 3) Cirrhosis (Knodell et al., 1981). The preferred Batts-Ludwig and Scheuer classification of fibrosis is divided into four phases; 1) Expansion of the fibrous portal, 2) Portal-portal septa periportal fibrosis, 3) Cirrhosis with bridging fibrosis but no apparent cirrhosis, and 4) Fibrous septa around regenerative nodules (Locke et al., 1996). On the Ishak scale fibrosis stages run from 0 to 6; 0: No fibrosis, 1: Fibrous growth of certain portal regions, with or without short fibrous septa, 2: Most portal locations have fibrous expansion with or without short fibrous septa, 3:

Fibrous growth of most portal locations, including portal-to-portal bridging on occasion, 4: Fibrous portal area extension with distinct portal-portal and portal-central bridging, 5: Distinctive bridging with occasional nodules (incomplete cirrhosis) and 6: Cirrhosis, either probable or certain (Ishak et al., 1995).

1.1. Symptoms and complications

Hepatic fibrosis does not generate symptoms on its own. But in most clinical situations such as(recurrent episodes of severe acute alcoholic hepatitis, subfulminant hepatitis, and fibrosing cholestasis in patients with HCV reinfection after liver transplantation) it develops into cirrhosis (Berenguer et al., 2003). Cirrhosis develops in most individuals after 15–20 years. Cirrhosis-related clinical consequences include ascites, renal failure, hepatic encephalopathy, and variceal hemorrhage. Cirrhotic patients can be free of serious problems for many years (compensated cirrhosis). Decompensated cirrhosis is linked with a low survival rate, and liver transplantation is frequently recommended as an alternative viable treatment(Davis et al., 2003). it is also associated with an increased chance of developing hepatocellular cancer.

2. Cell types are involved in the liver fibrosis progression.

Recent investigations have revealed that extracellular matrix accumulation during chronic liver fibrosis is driven by a heterogeneous population of cells (Elpek, 2014).

2.1. Hepatic stellate cells (HSCs)

Hepatic stellate cells serve as the most abundant kind of cells associated with liver fibrosis. HSCs are quiescent in normal livers, dwell in the Disse area, store vitamin A in lipid droplets, and act as liver pericytes(Dhar et al., 2020). HSCs shed lipid droplets, develop into myofibroblasts, and express less of the genes glial fibrillary acidic protein and peroxisome proliferator-activated receptor gamma (PPAR-γ) in response to chronic liver injury. The expression of fibrogenic genes such as alpha-smooth muscle actin (α-SMA) and collagen I starts in myofibroblasts. They spread out and relocate to the area of liver injury, producing ECM there(Acharya et al., 2021). Vascular endothelial growth factor

(VEGF), which is also produced by myofibroblasts, directly promotes HSC proliferation(Duffy et al., 2004).

2.2. Inflammatory cells and cytokines

Inflammation brought on by acute liver damage is beneficial for encouraging hepatic regeneration. On the other hand, chronic inflammation is damaging and contributes significantly to the etiology of liver fibrosis. Inflammatory cells such as (neutrophils, Kupffer cells, liver resident macrophages, bone marrow-derived monocytes, and Th17) cells can activate HSCs by secreting cytokines and growth factors, according to in vitro and in vivo studies(Seki & Schwabe, 2015). Transforming growth factor (TGF-β), which is crucial for liver fibrogenesis, is mostly produced by liver macrophages, particularly Kupffer cells(Dooley & ten Dijke, 2012). TGF-β binds to its receptor in HSCs, promoting myofibroblast activation and collagen Types I and III production. Therefore, it has been shown that blocking TGF-β or its genetic deletion, reduces liver fibrosis(Dewidar et al., 2019). Th17 cells release IL-17, a profibrogenic cytokine, it was reported that inhibiting IL-17 signaling prevents the development of liver fibrosis(Tan et al., 2013). Another fibrogenic cytokine, chemokine (C-C motif) ligand 2 (CCL2) which is generated by macrophages in response to liver injury increases HSC activation in the liver (Saiman & Friedman, 2012).

Platelet-derived growth factor (PDGF) is a strong mitogen for HSCs that is secreted by macrophages. The development of liver fibrosis and HSC activation have both been shown to depend on the PDGF signaling pathway. When the liver is injured, neutrophils and activated Kupffer cells release reactive oxygen species (ROS), which encourages HSC activation (Ramos-Tovar & Muriel, 2020; Ying et al., 2017). Notably, macrophages not only induce liver fibrosis but can also assist in fibrosis recovery by inducing myofibroblast apoptosis and phagocytizing apoptotic cells (Ramos-Tovar & Muriel, 2020). Furthermore, they release matrix metalloproteinases such as MMP9, MMP12, and MMP13, which destroy ECM, a critical component in fibrosis resolution. MMP activation reduces the expression of tissue inhibitors of metalloproteinases (TIMP1). TIMP1 promotes HSC activation and survival (Cabral-Pacheco et al., 2020).

2.3. Liver sinusoidal endothelial cells (LSECs)

Liver sinusoidal endothelial cells (LSECs) are required for nutrition transport, lymphocyte recruitment from the bloodstream, cytokine, and growth factor release, and have been shown to keep HSCs dormant in healthy livers (Wilkinson et al., 2020). LSECs produce nitric oxide synthase (eNOS) which is crucial for LSECs' physiological phenotypic maintenance, inhibiting HSC activation, and facilitating the conversion of active HSCs to quiescence(Xie et al., 2012). As a result, the gatekeeper function that stimulates HSCs quiescence entrance is missing in the LSECs of the injured liver. After the rupture of endothelial cells, LSECs release profibrogenic cytokines such as TGF-1, PDGF, interleukins, tumor necrosis factor (TNF), and VEGF. These cytokines attract inflammatory cells and activate HSCs at the site of damage (Yang & Zhang, 2021).

3. Experimental models for studying liver fibrosis in rats

There has been extensive research on how fibrosis and liver cirrhosis are established in both animals and people. Several in vitro and in vivo studies have been conducted to investigate the pathophysiology and molecular mechanisms involved in liver fibrosis as well as the potential protective and treatment measures.

3.1. Chemical-based models

Since many different drugs are known to cause liver fibrosis, they are commonly used to induce liver fibrosis in experimental animal models such as:

3.1.1. Ethanol-induced liver fibrosis

Hepatic steatosis is the most typical sign of alcoholic liver disease (ALD), which can result in fibrosis and cirrhosis. The primary metabolizers of ethanol in the liver are alcohol dehydrogenases and CYP450 enzymes. This mechanism is linked to the production of reactive oxygen species (ROS), glutathione depletion, lipid peroxidation, activation of HCS, and increased collagen synthesis (Beier & McClain, 2010; Lieber, 1997). The two mouse strains that are used in ALD research the most frequently are HAP-2 and C57BL/6. Compared to rats, mice are more likely to get alcohol-induced liver fibrosis, with female mice being the

most susceptible (Melon et al., 2013; Shinohara et al., 2010). However, no rodent model completely mimics the effects of alcohol use on ALD in humans. To get around these restrictions, other techniques have been devised, including combining the administration of ethanol with a second stimulus such as a specialized diet, pharmacological agents, CYP450 inducers, hormones, Toll-like receptor ligands, genetic alteration, or viral infection. However, several factors influence these combinational models, which may make it challenging to comprehend the findings (Brandon-Warner et al., 2012; Enomoto et al., 1998).

3.1.2. Carbon tetrachloride (CCl4)-induced liver fibrosis

The most popular hepatotoxin utilized in rodent models of liver fibrosis and cirrhosis is carbon tetrachloride (CCl4). It resembles chronic illness and toxic damage in humans in many ways. CCl4 biotransformation in the liver results in based on CYP2E1 and trichloromethyl radical that is used in the processes of lipid peroxidation and free radical reactions (Basu, 2003; Weber et al., 2003)which are responsible for an acute-phase reaction that is represented by a significant increase in collagen fiber content, centrilobular hepatocytes necrosis, Kupffer cells activation and the stimulation of inflammation (EL Sayed et al., 2019; Heindryckx et al., 2009). Both rats and mice can be used in the CCl4 model. Mice, on the other hand, are favored because they have a greater CCl4 metabolic rate than rats (Wallace et al., 2015). For induced liver fibrosis CCl4 is injected intraperitoneally 2–3 times per week for 4–6 weeks at a dosage range of 300–1000 μl/kg (Constandinou et al., 2005).

There is a lot of controversy around the oral injection of CCl4, as some researchers assert it has shown the highest repetition of liver fibrosis with a tolerable animal survival rate (Jang et al., 2008), Others, on the other hand, do not suggest oral delivery unless necessary due to high risks of early fatality (Scholten et al., 2015). Subcutaneous injection reduces the death of mice. However, animals develop granulomas at the injection site (Domenicali et al., 2009). Although inhalation administration has several drawbacks, such as the need for specialized equipment and operator training, it has been characterized as the ideal model for studying cirrhosis consequences such as portal hypertension and ascites development (Liedtke et al., 2013).

3.1.3. Thioacetamide-induced liver fibrosis

Thioacetamide must go through metabolic activation to be toxic. This bioactivation process driven by CYP450 isoenzymes, results in the synthesis of thioacetamide sulfur dioxide, which is responsible for the overall toxicity. Although the mechanisms by which thioacetamide sulfur dioxide induces liver fibrosis are unknown, they may be explained by several processes, including the breakdown of methionine by reducing enzymes, an increase in lipid peroxidation, and an increase in oxidative stress by activating relevant proteins (El-Gendy et al., 2021). Regardless, the outcome is severe oxidative damage associated with HSC activation. Mice are also frequently employed, even though rats are the ideal species for creating thioacetamide-mediated liver fibrosis models. Thioacetamide is often administered intraperitoneally, three times per week for 6-8 weeks, at doses of 100 to 200 mg/kg body weight. The livers of these animals become enlarged, with centrilobular necrosis and moderate inflammatory cell infiltration, as well as upregulation of serum levels of alanine (ALT) and aspartate aminotransferase(AST) (Crespo Yanguas et al., 2016). The dosage in this model has recently been established at 150 mg/kg three times per week for a period of 8 to 12 weeks. Higher dosages of 200–300 mg/kg body weight are utilized for 16 weeks when given orally. Furthermore, when given 300 mg/l in drinking water, C57BL/6 mice take 2–4 months to develop substantial fibrosis (Wallace et al., 2015).

3.1.4. Dimethyl nitrosamine (DMN) and diethyl nitrosamine (DEN) - induced liver fibrosis

Dimethyl nitrosamine (DMN) and diethyl nitrosamine (DEN) are carcinogenic chemicals commonly employed in animal studies to induce liver fibrosis. ROS resulting from their biotransformation react with nucleic acids, proteins, and lipids in a variety of ways producing cell dysfunction and the onset of centrilobular necrosis (Aparicio-Bautista et al., 2013; Aydın & Akçalı, 2018; Oh et al., 2009; Sánchez-Pérez et al., 2005). The R16 strain of rats is the most vulnerable to carcinogenic substances (Melhem et al., 1989). DEN dosage orally is once a week for 3–11 weeks or intraperitoneally once a week for 2 weeks at dosages ranging from 40 to 100 mg/kg (Delire et al., 2015; Jin et al., 2010).

3.2. Diet-based models

Several diet-based models have been established for inducing liver fibrosis. However, results from these diet-based models cannot be extrapolated across species since they do not accurately reflect the typical features of human illness (Anstee & Goldin, 2006).

3.2.1. High-fat diet HF)-induced liver fibrosis

The mice in this paradigm put on weight and become insulin-resistant in their peripheral tissues. it takes 50 weeks to develop steatohepatitis with only minimal fibrosis(Ito et al., 2007). The most ideal rodents to develop steatohepatitis on an HF diet are male inbred C57BL/6 mice(Ganz et al., 2014). On the other hand, rats are not responsive to HF diets. This high-cholesterol diet induces fibrotic steatohepatitis in 9 weeks (Ichimura et al., 2015).

3.2.2. Methionine and choline-deficient diet (MCD)-induced liver fibrosis

The most used model to research nonalcoholic steatohepatitis (NASH) is the MCD diet (Rinella & Green, 2004). MCD diets imitate the hepatic stress brought on by the transfer of fatty acids from adipose tissue to the liver and the rise in triglyceride synthesis, which leads to liver steatosis and lipotoxicity (Betoule et al., 2014). Kupffer cells are the first to respond to hepatocyte injury, hence they may be involved in the beginning and development of MCD diet-induced liver steatosis (Tosello-Trampont et al., 2012). Activated Kupffer cells produce more TNF, attract more monocytes, and may inhibit the deposition of collagen by secreting a lot of MMP-13 (Sun et al., 2013). These macrophages can also upregulate pro-inflammatory pathways and mediators, such as nuclear factor kappa-light-chain-enhancer of activated B cells, intracellular adhesion molecule 1, cyclooxygenase 2, monocyte chemoattractant protein-1, and IL6 (Orozco-Solis et al., 2015). As a result, the pathology progresses into a more fibrotic stage as a result of activated HSCs. Steatohepatitis manifests in mice fed an MCD diet after 8 weeks, although the more fibrotic stage, specifically affecting the portal and bridging sections, is not seen until 16 weeks (Itagaki et al., 2013).

3.2.3. Choline-deficient l-amino acid-defined diet

The choline-deficient l-amino acid-defined diet results in weight gain and peripheral insulin resistance in animals (De Minicis et al., 2014; Denda et al., 2002). These models are suitable for studying the development from nonalcoholic fatty liver diseases (NAFLD) to nonalcoholic steatohepatitis (NASH) and then to hepatocellular carcinoma (HCC) since choline-deficient l-amino acid-fed rats and C57BL/6J mice typically develop liver cancers linked to fibrosis (Denda et al., 2002; Nakae et al., 1992). After 22 weeks and 84 weeks, mice fed this diet exhibit clear-cut liver fibrosis (Denda et al., 2002).

3.3. Surgery-based models

It is widely established that common bile duct ligation (BDL) can lead to periportal biliary fibrosis and cholestatic damage. This model was developed in rats first, and then it was used with mice (Miyoshi et al., 1999; Rodriguez-Garay et al., 1996). As a result, BDL consists of a bile duct that has been transected twice between ligatures The bile duct blockage causes an increase in B and T lymphocytes in the portal tracts, which leads to the production of ROS and liver damage (Georgiev et al., 2008; Rodriguez-Garay et al., 1996). BDL is particularly useful for investigations of liver fibrosis brought on by cholestatic damage over a short period (Chang et al., 2005; Iwaisako et al., 2014; Park et al., 2014).

3.4. Genetically- modified models

Over the past ten years, genetically altered animals have developed into potent study models. They make it possible to learn more about how certain proteins and signaling pathways contribute to the development of liver fibrosis, which makes it easier to find potential novel therapeutic targets (Hayashi & Sakai, 2011). Nevertheless, genetic models require a second trigger to cause illness since the genetic alteration alone seldom results in liver fibrosis This suggests that the environment and genetics interact to cause the illness to appear (Larter & Yeh, 2008). The genetically- modified models include Multidrug resistance-associated protein 2-deficient mice-induced liver fibrosis, Alms1Fat ausi mutant mice (Morita et al., 2013) , and Alms1Fat ausi mutant mice (Arsov et al., 2006).

3.5. Infection-based models

Due to the strong similarity to human infection and good repeatability, Schistosoma mansoni infection is easily established in mice. The C3H/HeN strain of mice is the most likely to acquire greater degrees of fibrosis, but other mouse strains can exhibit significant variability in hepatic fibrosis levels. As an alternative, animals can be infected by injecting 10.000 viable eggs or 35 cercariae intravenously (Cheever et al., 1987; Cheever et al., 2002) or percutaneously through the tail (Chiaramonte et al., 2001). More than 100 eggs can be laid daily by mature cercariae, some of which can be caught in the liver. This is the primary reason why liver fibrosis-related granulomas develop (Chiaramonte et al., 2001).

4. Pathophysiology of liver fibrosis

4.1. Role of oxidative stress (OS) in liver fibrosis

The condition in which the cellular pro-oxidant/antioxidant redox equilibrium alters in favor of the pro-oxidant state is known as oxidative stress. OS can be caused by an increase in reactive oxygen species (ROS) or reactive nitrogen species (RNS), as well as a decrease in antioxidant production (Sies & Cadenas, 1985). ROS or RNS produced by mitochondria, endoplasmic reticulum, and peroxisomes damage lipids, proteins, and DNA, promotes hepatocyte necrosis and apoptosis, and increase the inflammatory response. They also increase Kupffer cell and circulating inflammatory cell production of profibrogenic mediators and directly activate hepatic stellate cells(Ha et al., 2010).

To combat free radicals, cells engage with the antioxidant response element (ARE) and several redox-sensitive transcription factors including nuclear factor (NF)-ĸB in response to ROS or RNS. Nuclear factor erythroid 2-related factor 2 (NRF2) is one of the responsible elements for controlling the expression of protective genes that maintain redox homeostasis within the cell (Kobayashi & Yamamoto, 2005). Nrf2 is found in the cytosol sequestered by Kelch-like ECH-associated protein 1 (Keap1) under physiological conditions and is released and translocates into the nucleus upon exposure to ROS or electrophilic chemicals. Within the nucleus, Nrf2 binds to the antioxidant response element (ARE) and promotes the transcription of many cytodefensive and antioxidant factors,

including heme oxygenase 1 (HO-1), superoxide dismutase (SOD), and others (Luedde et al., 2011). Upregulation of Nrf2/HO-1 signaling has been associated with decreased collagen deposition in the liver of rat models of fibrosis and HCC(Khadrawy et al., 2021; Mahmoud et al., 2017).

4.2. Role of inflammation in liver fibrosis

The main cell types involved in the inflammatory process in liver fibrosis are monocytes and macrophages which are responsible for producing large amounts of nitric oxide (NO) and inflammatory cytokines such as tumor necrosis factor α (TNFα) which have a direct stimulatory effect on stellate cell collagen synthesis (Weiskirchen & Tacke, 2014).

Some of the inflammatory cytokines involved in liver fibrosis are IL-1β, TNF-α, TGF – β, and IL- 6; IL-1β mediates up-regulation of fibrogenic tissue, TNF-α contributes to hepatocyte apoptosis, immune cell activation, and HSC activation, TGF–β1 plays a role in fibrosis, contributing to both influx and activation of inflammatory cells as well as activation of SC. it is produced by Kupffer cells and SC, it up-regulates the transcription of the collagen genes and induces the expression of TIMP-1, and IL- 6 which is produced by hepatic SC from normal or cirrhotic livers, it up-regulates the expression of TGF-β in HSC from cirrhotic livers(Friedman, 1997).

5. Management of liver fibrosis

The best way to treat the condition is usually thought to be to remove the underlying stimulus (Bataller & Brenner, 2001; Li & Friedman, 1999). The only approach that has been proven to be genuinely beneficial in the past for treating hepatic fibrosis and severe cirrhosis is transplantation (Iredale, 2001). However, transplantation puts patients at significant risk for postoperative complications (Pirat et al., 2004). As a result, research into alternate strategies to stop liver fibrosis at an earlier stage is now being conducted (Bucuvalas & Ryckman, 2002).

5.1. Role of antioxidants and anti-inflammatory agents in liver fibrosis management

Previous several studies have been conducted to investigate the antifibrotic effects of several agents such as Prednisone (Czaja & Carpenter, 2004; Mathurin et al., 1996), Colchicin (Morgan et al., 2005), ursodeoxycholic acid + methotrexate (Kaplan et al., 2004), Malotilate (Ryhanen et al., 1996), Octreotide (Fort et al., 1998) and IL-1 receptor antagonists(Mancini et al., 1994). These agents have been studied as anti-inflammatory agents depending on their ability to affect inflammatory cells that contribute to fibrosis, such as neutrophils and lymphocytes. In addition to antioxidant agents such as Vitamin E/C (Harrison et al., 2003), Silymarin (Jia et al., 2001), Dilineolylphosphatidylcholine (Cao et al., 2002), N-acetylcysteine (Kim et al., 2001), S-adenosyl-L-methionine (Mato et al., 1999)and Polyenylphosphatidylcholine(Lieber et al., 2003). They also have been investigated due to their ability to decrease oxidative stress and stimulation of antioxidant elementary genes.

5.2. Cytokine and signal-transduction based therapies

Liver fibrogenesis and the development of fibrosis have been linked to several cytokines and cellular signaling pathways such as TGF-β receptor competitors (Kondou et al., 2003), Halofuginone (Van de Casteele et al., 2004), Hepatocyte growth factor (Ozaki et al., 2002), Interferon-α Interferon-γ (Baroni et al., 1996), AT receptor inhibitors (losartan, olmesartan) (Castano et al., 2003), ACE inhibitors (peridinopril, captopril) (Wang et al., 2000) and TNP-470 Carbenoxolone (Uyama et al., 2003).

5.3. Herbal medicines

Asian nations have traditionally employed conventional drugs such as Sho-Saiko-to (TJ-9) (Oakley et al., 2005), Inchin-ko-to (TJ-135) (Dekel et al., 2003), Glycyrrhizin (Watanabe et al., 2001) , and Han-dan-gable (Li et al., 2003). These drugs have been studied to treat liver fibrosis, and new research both in vivo and in vitro has started to unravel the underlying molecular mechanism.

6. Low-level laser therapy

Low-Level Laser thereby (LLLT) is a special type of laser that affects biological systems through non-thermal means. This area of investigation started with the work of Mester et al in 1967. According to Posten et al, the properties of low-level lasers are a) Power output of lasers being 0.001- 0.1 Watts. b) Wavelength in the range of 300-10,600 nm. c) Pulse rate from 0, meaning continuous to 5000 Hertz (cycles per second). d) Intensity of 0.01-10 W/cm2 and dose of 0.01 to 100 J/ cm2 (Posten et al., 2005).

The wavelengths range from (600nm-1100nm) and fall inside the therapeutic optical window (S. Farivar et al., 2014; Huang et al., 2009). laser wavelengths from 600-700 nm are applied to treat superficial tissue targets. They have a lower penetration rate whereas deeper-seated tissues are treated with laser wavelengths between 780 and 950 nm because they may reach deeper layers of tissue (H. Chung et al., 2012). To achieve good therapeutic effects, optimal optical therapy procedures, comprising illumination parameters (such as wavelength, fluence(J/cm2), power density(mW/cm2), and pulse structure) must be chosen (Hashmi et al., 2010).

6.1. Applications of low-level laser therapy

Low-level laser therapy (LLLT), is among the novel approaches for preventing and treating several ailments, including muscle injury (Jówko et al., 2019), skin injury healing (Hartmann et al., 2021), acute lung injury (de Lima et al., 2013), and others. PBMT is the process by which LLLT modulates cellular function without causing significant tissue-level heating and has been used since the mid-1960s for inflammatory conditions (Mester, 1966). The interaction of LLLT with the cells includes different biomolecules such as transcription factors. LLLT has been suggested to increase mitochondrial ATP production and modulate ROS generation and the activity of transcription factors controlling cell proliferation and migration, cytokines, growth factors, tissue oxygenation, and protein synthesis (A. C. Chen et al., 2011; Hawkins et al., 2005; Yu et al., 2003). Amelioration of oxidative stress and inflammation has been implicated in the therapeutic effects of LLLT. In murine cortical neurons challenged with hydrogen peroxide, rotenone, or cobalt chloride, LLLT reduced mitochondrial ROS generation and cell death (Huang et al., 2013). LLLT prevented oxidative

stress and reduced collagen deposition in rat-traumatized Achilles tendons (Fillipin et al., 2005). The acute inflammatory response provoked by traumatic muscle injury in rats has been attenuated by LLLT (Silveira et al., 2016). In a murine model of CCl4-induced liver cirrhosis, LLLT ameliorated liver function and reduced the number of cirrhotic areas and inflammatory infiltrations (Oliveira-Junior et al., 2013).

6.2. Mechanism of cellular response to low-level laser therapy

6.2.1. Mitochondrial Respiration and ATP

The electron transport chain's complex IV contains mitochondrial cytochrome c oxidase (CCO), which exists in two states: oxidized and reduced, with absorption spectra in the red and near-infrared. It is a complex enzyme, consisting of many polypeptide subunits (I, II, and III). Two heme groups (a and a3) and a redox-active copper site, CuB, are found in subunit I, whereas the cytochrome c binding site and another redox-active copper site, CuA, are found in subunit II (Cooper et al., 1991). CCO reduces molecular oxygen to water by utilizing electrons provided by Cytochrome c. In reality, Karu had earlier postulated that the photon recipient was a constituent of the mitochondrial respiratory chain (Karu, 1989). Utilizing a comparison of the generalized spectra and spectroscopic data for CCO, Karu, and Afanas'eva suggested that the 820nm and 620nm bands were associated with the oxidized CUA, the 760 bands, and 680nm with the reduced CuB. The electron transport processes in mitochondria are accelerated by CCO stimulation, which eventually affects molecular and cellular alterations. The common chemicals impacted by CCO excitation are reactive oxygen species (ROS), adenosine triphosphate (ATP), and nitric oxide (NO) (Karu, 2010).

The nucleotide adenosine triphosphate (ATP) plays a variety of vital functions in the cell, including powering most of its energy-intensive processes and controlling several metabolic pathways. ATP activates intracellular pathways including MAPKs (mitogen-activated protein kinases) and FGF2 (growth factors like fibroblastic growth factor 2), EGF (epidermal growth factor), and NGF (nerve growth factor). It also regulates the concentration of ATP-driven carriers for ions such as Na+/K+ ATPase and calcium ion pumps as well as cyclic adenosine monophosphate (cAMP) (Karu, 2010). In a different investigation,

they established that 810nm-wavelength light boosted neurite outgrowth, and they showed that this stimulation was brought on by more ATP serving as a signaling molecule through P2Y receptors. These results imply that the response of cells to light may be significantly influenced by G protein–coupled membrane receptors (Anders et al., 2008).

6.2.2. Cellular Signaling Response to Low-level Laser Therapy.

Cells react to elevated ROS concentrations by producing scavenging antioxidants, modifying proteins, and expressing genes through a variety of molecules with ROS-detecting systems that can start signal transduction pathways through transcription factors (Aaron CH Chen et al., 2011). Some of the transcription factors that are regulated by these changes in mitochondrial respiration are (Ref1), (AP1), a heterodimer of c-Fos and c-Jun, (NF KB), p53, (ATF/CREB), (HIF1), and HIF-like factor (Hoon Chung et al., 2012; Shirin Farivar et al., 2014). When these factors are activated, proteins that have roles in cell proliferation, tissue oxygenation, and cytokine regulation, as well as growth factors and other inflammatory mediators, are synthesized (Hoon Chung et al., 2012). Previous research suggested that laser therapy decreased one of the isoforms of NOS and decreased levels of NO in the local tissues (Moriyama et al., 2005).

6.2.3. Molecular Signaling Response to Low-level Laser Therapy

A lot of studies have been published on the impact of laser treatment on gene expression. laser influenced 111 genes. This category comprised an increase in the expression of genes involved in energy metabolism, the respiratory chain, and cell proliferation (Masha et al., 2013). Previous research has shown that laser thereby promotes axonal regeneration after damage while decreasing inflammatory cell invasion/activation. they also discovered that the RNA expression of proinflammatory cytokine genes (TNF, IL1, and IL6) was suppressed while the RNA expression of the anti-inflammatory gene TGF increased (Byrnes et al., 2005).

Nuclear factor erythroid-2 related factor 2 (Nrf2) is a critical component in controlling the oxidative stress response. Nrf2 interacts with the cytoplasmic

protein Kelch-like ECH-associated protein-1 (Keap1) in the absence of stress (McMahon et al., 2003). then Keap1's conformation is altered as a result of exposure to too many free radicals, and Nrf2 is released. The free Nrf2 in the cytoplasm can then be translocated to the nucleus, where it binds to ARE (antioxidant response element)-mediated gene transcription, encoding detoxification antioxidant enzymes such as heme oxygenase (HO-1), NAD(P)H: quinine oxidoreductase 1 (NQO1), and glutamate-cysteine ligase catalytic subunit (GCLC), and thus perform cytoprotective (Itoh et al., 2004). After exposure to radiation at 635 nm, Sohn et al. observed that Nrf2 gene expression had increased [186]. Similar results were obtained by Trotter et al. (Sohn et al., 2015). who discovered that the application of blue light increased Nrf2 expression in vitro by a significant amount. Since this acts as a feedback mechanism after NF-kB activation, the interaction of these two pathways may be crucial in the PBM modulation of chronic inflammatory diseases. However further research will be needed to properly understand how blue and green light affect the Nrf2 signal (Trotter et al., 2017).

Nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) In its inactive state IκB is bound to NF-κB in the cytoplasm, however, once phosphorylated, IκB dissociates from NF-κB and is targeted to the proteasome for degradation. This permits free NF-κB to translocate to the nucleus and bind to DNA, triggering a cascade of gene transcription modifications, mRNA creation, and possible downstream expression of important cytokines, chemokines, and growth factors such as interleukin-8 (IL-8), IL-6, and vascular endothelial growth factor (VEGF102–105) (Curra et al., 2015). Light regulation of NF-κB has been reported by a variety of studies. For example, Chen et al. reported that 810 nm irradiation and radiant exposure of 0.003 J cm2 stimulated NFκB activation. Curra et al. investigated the effects of a 660 nm diode laser on NFκB protein levels in an in vivo hamster model of oral mucositis(Hamblin, 2017).

peroxisome proliferator-activated receptor gamma (PPAR-γ) plays an important function in decreasing inflammation by producing the anti-inflammatory heat shock protein 70 (HSP-70) (Croasdell et al., 2015). Lima and colleagues published research in which rats were exposed to 660 nm light (5.4 J) on the skin

above the bronchus (chest). They discovered a significant increase in PPAR mRNA expression following LLLT treatment, as well as enhanced PPAR-γ activity in bronchoalveolar lavage (BALF) cells from laser-treated mice. Lima concluded that LLLT can operate as a homeostatic facilitator by raising the expression of a transcription factor that signals the manufacture of HSP70 and other anti-inflammatory proteins (de Lima et al., 2013).

7. Conclusion

In summary, laser-tissue interaction involves reflection, refraction, scattering, and absorption, which are influenced by the presence of chromophores in tissues. Low-level laser therapy (LLLT) has emerged as a promising approach for various conditions due to its ability to modulate cellular functions without significant tissue heating. LLLT affects cellular responses through mechanisms such as mitochondrial respiration and ATP production, cellular signaling pathways, and molecular signaling responses.

At the mitochondrial level, LLLT stimulates cytochrome c oxidase (CCO), leading to increased ATP production and modulation of reactive oxygen species (ROS) generation. This ATP serves as a signaling molecule, influencing various intracellular pathways and cellular functions. LLLT also affects cellular signaling responses by regulating transcription factors involved in cell proliferation, tissue oxygenation, cytokine regulation, and inflammatory mediators.

Moreover, LLLT has been shown to influence gene expression, promoting energy metabolism, respiratory chain function, and cell proliferation while suppressing pro-inflammatory cytokines. Additionally, LLLT activates nuclear factor erythroid-2 related factor 2 (Nrf2), which plays a crucial role in the oxidative stress response and cytoprotection. Furthermore, LLLT modulates nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), peroxisome proliferator-activated receptor gamma (PPAR-γ), and other transcription factors, contributing to its anti-inflammatory effects and potential therapeutic benefits.

Overall, the diverse mechanisms of action of LLLT highlight its potential for treating various ailments by influencing cellular functions, signaling pathways, and gene expression patterns. Further research is needed to fully understand the specific effects and optimize the therapeutic applications of LLLT.

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Declarations

Conflict of interest The authors declare no conflict of interest.
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References

Acharya, P., Chouhan, K., Weiskirchen, S., & Weiskirchen, R. (2021). Cellular Mechanisms of Liver Fibrosis [Review]. *12*. https://doi.org/10.3389/fphar.2021.671640

Anders, J. J., Romanczyk, T. B., Ilev, I. K., Moges, H., Longo, L., Wu, X., & Waynant, R. W. J. I. J. o. S. T. i. Q. E. (2008). Light supports neurite outgrowth of human neural progenitor cells in vitro: the role of P2Y receptors. *14*(1), 118-125.

Anstee, Q. M., & Goldin, R. D. (2006). Mouse models in non-alcoholic fatty liver disease and steatohepatitis research. *Int J Exp Pathol*, *87*(1), 1-16. https://doi.org/10.1111/j.0959-9673.2006.00465.x

Aparicio-Bautista, D. I., Pérez-Carreón, J. I., Gutiérrez-Nájera, N., Reyes-Grajeda, J. P., Arellanes-Robledo, J., Vásquez-Garzón, V. R., Jiménez-García, M. N., Villa-Treviño, S. J. B. e. B. A.-P., & Proteomics. (2013). Comparative proteomic analysis of thiol proteins in the liver after oxidative stress induced by diethylnitrosamine. *1834*(12), 2528-2538.

Arsov, T., Larter, C. Z., Nolan, C. J., Petrovsky, N., Goodnow, C. C., Teoh, N. C., Yeh, M. M., & Farrell, G. C. (2006). Adaptive failure to high-fat diet characterizes steatohepatitis in Alms1 mutant mice. *Biochem Biophys Res Commun*, *342*(4), 1152-1159. https://doi.org/10.1016/j.bbrc.2006.02.032

Aydın, M. M., & Akçalı, K. C. J. T. T. J. o. G. (2018). Liver fibrosis. *29*(1), 14.

Baroni, G. S., D'Ambrosio, L., Curto, P., Casini, A., Mancini, R., Jezequel, A. M., & Benedetti, A. (1996). Interferon gamma decreases hepatic stellate cell activation and extracellular matrix deposition in rat liver fibrosis. *Hepatology*, *23*(5), 1189-1199. https://doi.org/10.1002/hep.510230538

Basu, S. (2003). Carbon tetrachloride-induced lipid peroxidation: eicosanoid formation and their regulation by antioxidant nutrients. *Toxicology*, *189*(1-2), 113-127. https://doi.org/10.1016/s0300-483x(03)00157-4

Bataller, R., & Brenner, D. A. (2001). Hepatic stellate cells as a target for the treatment of liver fibrosis. *Semin Liver Dis*, *21*(3), 437-451. https://doi.org/10.1055/s-2001-17558

Beier, J. I., & McClain, C. J. (2010). Mechanisms and cell signaling in alcoholic liver disease. *Biol Chem*, *391*(11), 1249-1264. https://doi.org/10.1515/BC.2010.137

Berenguer, M., Prieto, M., Palau, A., Rayon, J. M., Carrasco, D., Juan, F. S., Lopez-Labrador, F. X., Moreno, R., Mir, J., & Berenguer, J. (2003). Severe recurrent hepatitis C after liver retransplantation for hepatitis C virus-related graft cirrhosis. *Liver Transpl*, *9*(3), 228-235. https://doi.org/10.1053/jlts.2003.50029

Berumen, J., Baglieri, J., Kisseleva, T., & Mekeel, K. (2021). Liver fibrosis: Pathophysiology and clinical implications. *WIREs Mech Dis*, *13*(1), e1499. https://doi.org/10.1002/wsbm.1499

Betoule, M., Kessler, R., Guy, J., Mosher, J., Hardin, D., Biswas, R., Astier, P., El-Hage, P., Konig, M., Kuhlmann, S. J. A., & Astrophysics. (2014). Improved cosmological constraints from a joint analysis of the SDSS-II and SNLS supernova samples. *568*, A22.

Brandon-Warner, E., Schrum, L. W., Schmidt, C. M., & McKillop, I. H. (2012). Rodent models of alcoholic liver disease: of mice and men. *Alcohol*, *46*(8), 715-725. https://doi.org/10.1016/j.alcohol.2012.08.004

Bucuvalas, J. C., & Ryckman, F. C. (2002). Long-term outcome after liver transplantation in children. *Pediatr Transplant*, *6*(1), 30-36. https://doi.org/10.1034/j.1399-3046.2002.1r058.x

Byrnes, K. R., Waynant, R. W., Ilev, I. K., Wu, X., Barna, L., Smith, K., Heckert, R., Gerst, H., Anders, J. J. J. L. i. S., Medicine, M. T. O. J. o. t. A. S. f. L., & Surgery. (2005). Light promotes regeneration and functional recovery and alters the immune response after spinal cord injury. *36*(3), 171-185.

Cabral-Pacheco, G. A., Garza-Veloz, I., Castruita-De la Rosa, C., Ramirez-Acuna, J. M., Perez-Romero, B. A., Guerrero-Rodriguez, J. F., Martinez-Avila, N., & Martinez-Fierro, M. L. (2020). The Roles of Matrix Metalloproteinases and Their Inhibitors in Human Diseases. *Int J Mol Sci*, *21*(24). https://doi.org/10.3390/ijms21249739

Cao, Q., Mak, K. M., & Lieber, C. S. (2002). DLPC decreases TGF-beta1-induced collagen mRNA by inhibiting p38 MAPK in hepatic stellate cells.

Am J Physiol Gastrointest Liver Physiol, *283*(5), G1051-1061. https://doi.org/10.1152/ajpgi.00128.2002

Castano, G., Viudez, P., Riccitelli, M., & Sookoian, S. (2003). A randomized study of losartan vs propranolol: Effects on hepatic and systemic hemodynamics in cirrhotic patients. *Ann Hepatol*, *2*(1), 36-40. https://www.ncbi.nlm.nih.gov/pubmed/15094704

Chang, M. L., Yeh, C. T., Chang, P. Y., & Chen, J. C. (2005). Comparison of murine cirrhosis models induced by hepatotoxin administration and common bile duct ligation. *World J Gastroenterol*, *11*(27), 4167-4172. https://doi.org/10.3748/wjg.v11.i27.4167

Cheever, A. W., Duvall, R. H., Hallack, T. A., Jr., Minker, R. G., Malley, J. D., & Malley, K. G. (1987). Variation of hepatic fibrosis and granuloma size among mouse strains infected with Schistosoma mansoni. *Am J Trop Med Hyg*, *37*(1), 85-97. https://doi.org/10.4269/ajtmh.1987.37.85

Cheever, A. W., Lenzi, J. A., Lenzi, H. L., & Andrade, Z. A. (2002). Experimental models of Schistosoma mansoni infection. *Mem Inst Oswaldo Cruz*, *97*(7), 917-940. https://doi.org/10.1590/s0074-02762002000700002

Chen, A. C., Arany, P. R., Huang, Y.-Y., Tomkinson, E. M., Sharma, S. K., Kharkwal, G. B., Saleem, T., Mooney, D., Yull, F. E., & Blackwell, T. S. J. P. o. (2011). Low-level laser therapy activates NF-kB via generation of reactive oxygen species in mouse embryonic fibroblasts. *6*(7), e22453.

Chen, A. C., Arany, P. R., Huang, Y. Y., Tomkinson, E. M., Sharma, S. K., Kharkwal, G. B., Saleem, T., Mooney, D., Yull, F. E., Blackwell, T. S., & Hamblin, M. R. (2011). Low-level laser therapy activates NF-kB via generation of reactive oxygen species in mouse embryonic fibroblasts. *PLoS One*, *6*(7), e22453. https://doi.org/10.1371/journal.pone.0022453

Chiaramonte, M. G., Cheever, A. W., Malley, J. D., Donaldson, D. D., & Wynn, T. A. (2001). Studies of murine schistosomiasis reveal interleukin-13 blockade as a treatment for established and progressive liver fibrosis. *Hepatology*, *34*(2), 273-282. https://doi.org/10.1053/jhep.2001.26376

Chung, H., Dai, T., Sharma, S. K., Huang, Y.-Y., Carroll, J. D., & Hamblin, M. R. J. A. o. b. e. (2012). The nuts and bolts of low-level laser (light) therapy. *40*(2), 516-533.

Chung, H., Dai, T., Sharma, S. K., Huang, Y. Y., Carroll, J. D., & Hamblin, M. R. (2012). The nuts and bolts of low-level laser (light) therapy. *Ann Biomed Eng*, *40*(2), 516-533. https://doi.org/10.1007/s10439-011-0454-7

Constandinou, C., Henderson, N., & Iredale, J. P. (2005). Modeling liver fibrosis in rodents. In *Fibrosis Research* (pp. 237-250). Springer.

Cooper, C. E., Nicholls, P., & Freedman, J. A. (1991). Cytochrome c oxidase: structure, function, and membrane topology of the polypeptide subunits. *Biochem Cell Biol*, *69*(9), 586-607. https://doi.org/10.1139/o91-089

Crespo Yanguas, S., Cogliati, B., Willebrords, J., Maes, M., Colle, I., Van den Bossche, B., de Oliveira, C. P. M. S., Andraus, W., Alves, V. A., & Leclercq, I. J. A. o. t. (2016). Experimental models of liver fibrosis. *90*(5), 1025-1048.

Croasdell, A., Duffney, P. F., Kim, N., Lacy, S. H., Sime, P. J., & Phipps, R. P. (2015). PPARgamma and the Innate Immune System Mediate the Resolution of Inflammation. *PPAR Res*, *2015*, 549691. https://doi.org/10.1155/2015/549691

Curra, M., Pellicioli, A. C., Filho, N. A., Ochs, G., Matte, U., Filho, M. S., Martins, M. A., & Martins, M. D. (2015). Photobiomodulation reduces oral mucositis by modulating NF-kB. *J Biomed Opt*, *20*(12), 125008. https://doi.org/10.1117/1.JBO.20.12.125008

Czaja, A. J., & Carpenter, H. A. (2004). Progressive fibrosis during corticosteroid therapy of autoimmune hepatitis. *Hepatology*, *39*(6), 1631-1638. https://doi.org/10.1002/hep.20235

Davis, G. L., Albright, J. E., Cook, S. F., & Rosenberg, D. M. (2003). Projecting future complications of chronic hepatitis C in the United States. *Liver Transpl*, *9*(4), 331-338. https://doi.org/10.1053/jlts.2003.50073

de Lima, F. M., Albertini, R., Dantas, Y., Maia-Filho, A. L., Santana Cde, L., Castro-Faria-Neto, H. C., Franca, C., Villaverde, A. B., & Aimbire, F. (2013). Low-level laser therapy restores the oxidative stress balance in acute lung injury induced by gut ischemia and reperfusion. *Photochem Photobiol*, *89*(1), 179-188. https://doi.org/10.1111/j.1751-1097.2012.01214.x

De Minicis, S., Agostinelli, L., Rychlicki, C., Sorice, G. P., Saccomanno, S., Candelaresi, C., Giaccari, A., Trozzi, L., Pierantonelli, I., Mingarelli, E., Marzioni, M., Muscogiuri, G., Gaggini, M., Benedetti, A., Gastaldelli, A., Guido, M., & Svegliati-Baroni, G. (2014). HCC development is associated to peripheral insulin resistance in a mouse model of NASH. *PLoS One*, *9*(5), e97136. https://doi.org/10.1371/journal.pone.0097136

Dekel, R., Zvibel, I., Brill, S., Brazovsky, E., Halpern, Z., & Oren, R. (2003). Gliotoxin ameliorates development of fibrosis and cirrhosis in a thioacetamide rat model. *Dig Dis Sci*, *48*(8), 1642-1647. https://doi.org/10.1023/a:1024792529601

Delire, B., Stärkel, P., Leclercq, I. J. J. o. c., & hepatology, t. (2015). Animal models for fibrotic liver diseases: what we have, what we need, and what is under development. *3*(1), 53.

Denda, A., Kitayama, W., Kishida, H., Murata, N., Tsutsumi, M., Tsujiuchi, T., Nakae, D., & Konishi, Y. (2002). Development of hepatocellular adenomas and carcinomas associated with fibrosis in C57BL/6J male mice given a choline-deficient, L-amino acid-defined diet. *Jpn J Cancer Res*, *93*(2), 125-132. https://doi.org/10.1111/j.1349-7006.2002.tb01250.x

Dewidar, B., Meyer, C., Dooley, S., & Meindl-Beinker, A. N. (2019). TGF-beta in Hepatic Stellate Cell Activation and Liver Fibrogenesis-Updated 2019. *Cells*, *8*(11). https://doi.org/10.3390/cells8111419

Dhar, D., Baglieri, J., Kisseleva, T., & Brenner, D. A. (2020). Mechanisms of liver fibrosis and its role in liver cancer. *Exp Biol Med (Maywood)*, *245*(2), 96-108. https://doi.org/10.1177/1535370219898141

Domenicali, M., Caraceni, P., Giannone, F., Baldassarre, M., Lucchetti, G., Quarta, C., Patti, C., Catani, L., Nanni, C., & Lemoli, R. M. J. J. o. h. (2009). A novel model of CCl4-induced cirrhosis with ascites in the mouse. *51*(6), 991-999.

Dooley, S., & ten Dijke, P. (2012). TGF-beta in progression of liver disease. *Cell Tissue Res*, *347*(1), 245-256. https://doi.org/10.1007/s00441-011-1246-y

Duffy, A. M., Bouchier-Hayes, D. J., Harmey, J. H. J. V., & Cancer. (2004). Vascular endothelial growth factor (VEGF) and its role in non-endothelial cells: autocrine signalling by VEGF. *2*, 133-144.

El-Gendy, Z., Ramadan, A., El-Batran, S., Ahmed, R., El-Marasy, S., Abd El-Rahman, S., Youssef, S. J. H., & Toxicology, E. (2021). Carvacrol hinders the progression of hepatic fibrosis via targeting autotaxin and thioredoxin in thioacetamide-induced liver fibrosis in rat. *40*(12), 2188-2201.

EL Sayed, H. E., Morsy, L. E., Abo Emara, T. M., & Galhom, R. A. J. T. E. J. o. H. M. (2019). Effect of carbon tetrachloride (CCl4) on liver in adult albino rats: histological study. *76*(6), 4254-4261.

Elpek, G. O. (2014). Cellular and molecular mechanisms in the pathogenesis of liver fibrosis: An update. *World J Gastroenterol*, *20*(23), 7260-7276. https://doi.org/10.3748/wjg.v20.i23.7260

Enomoto, N., Ikejima, K., Bradford, B., Rivera, C., Kono, H., Brenner, D. A., & Thurman, R. G. (1998). Alcohol causes both tolerance and sensitization of rat Kupffer cells via mechanisms dependent on endotoxin. *Gastroenterology*, *115*(2), 443-451. https://doi.org/10.1016/s0016-5085(98)70211-2

Farivar, S., Malekshahabi, T., & Shiari, R. (2014). Biological effects of low level laser therapy. *J Lasers Med Sci*, *5*(2), 58-62. https://www.ncbi.nlm.nih.gov/pubmed/25653800

Farivar, S., Malekshahabi, T., & Shiari, R. J. J. o. l. i. m. s. (2014). Biological effects of low level laser therapy. *5*(2), 58.

Fillipin, L. I., Mauriz, J. L., Vedovelli, K., Moreira, A. J., Zettler, C. G., Lech, O., Marroni, N. P., & Gonzalez-Gallego, J. (2005). Low-level laser therapy (LLLT) prevents oxidative stress and reduces fibrosis in rat traumatized Achilles tendon. *Lasers Surg Med*, *37*(4), 293-300. https://doi.org/10.1002/lsm.20225

Fort, J., Oberti, F., Pilette, C., Veal, N., Gallois, Y., Douay, O., Rousselet, M. C., Rosenbaum, J., & Cales, P. (1998). Antifibrotic and hemodynamic effects of the early and chronic administration of octreotide in two models of liver fibrosis in rats. *Hepatology*, *28*(6), 1525-1531. https://doi.org/10.1002/hep.510280612

Friedman, S. L. (1997). Molecular mechanisms of hepatic fibrosis and principles of therapy. *J Gastroenterol*, *32*(3), 424-430. https://doi.org/10.1007/BF02934504

Friedman, S. L. (2000). Molecular regulation of hepatic fibrosis, an integrated cellular response to tissue injury. *J Biol Chem*, *275*(4), 2247-2250. https://doi.org/10.1074/jbc.275.4.2247

Friedman, S. L. (2003). Liver fibrosis -- from bench to bedside. *J Hepatol*, *38 Suppl 1*, S38-53. https://doi.org/10.1016/s0168-8278(02)00429-4

Ganz, M., Csak, T., & Szabo, G. (2014). High fat diet feeding results in gender specific steatohepatitis and inflammasome activation. *World J Gastroenterol*, *20*(26), 8525-8534. https://doi.org/10.3748/wjg.v20.i26.8525

Georgiev, P., Jochum, W., Heinrich, S., Jang, J. H., Nocito, A., Dahm, F., & Clavien, P. A. (2008). Characterization of time-related changes after experimental bile duct ligation. *Br J Surg*, *95*(5), 646-656. https://doi.org/10.1002/bjs.6050

Gines, P., Castera, L., Lammert, F., Graupera, I., Serra-Burriel, M., Allen, A. M., Wong, V. W., Hartmann, P., Thiele, M., Caballeria, L., de Knegt, R. J., Grgurevic, I., Augustin, S., Tsochatzis, E. A., Schattenberg, J. M., Guha, I. N., Martini, A., Morillas, R. M., Garcia-Retortillo, M., . . . LiverScreen Consortium, I. (2022). Population screening for liver fibrosis: Toward early diagnosis and intervention for chronic liver diseases. *Hepatology*, *75*(1), 219-228. https://doi.org/10.1002/hep.32163

Ha, H. L., Shin, H. J., Feitelson, M. A., & Yu, D. Y. (2010). Oxidative stress and antioxidants in hepatic pathogenesis. *World J Gastroenterol*, *16*(48), 6035-6043. https://doi.org/10.3748/wjg.v16.i48.6035

Hamblin, M. R. (2017). Mechanisms and applications of the anti-inflammatory effects of photobiomodulation. *AIMS Biophys*, *4*(3), 337-361. https://doi.org/10.3934/biophy.2017.3.337

Harris, R., Harman, D. J., Card, T. R., Aithal, G. P., & Guha, I. N. (2017). Prevalence of clinically significant liver disease within the general population, as defined by non-invasive markers of liver fibrosis: a systematic review. *Lancet Gastroenterol Hepatol*, *2*(4), 288-297. https://doi.org/10.1016/S2468-1253(16)30205-9

Harrison, S. A., Torgerson, S., Hayashi, P., Ward, J., & Schenker, S. (2003). Vitamin E and vitamin C treatment improves fibrosis in patients with

nonalcoholic steatohepatitis. *Am J Gastroenterol*, *98*(11), 2485-2490. https://doi.org/10.1111/j.1572-0241.2003.08699.x

Hartmann, D., Martins, R., da Silva, T., Stefanello, S., Courtes, A., Gonçalves, D., Furtado, A., Duarte, B., Signori, L., Soares, F. J. B. J. o. M., & Research, B. (2021). Oxidative stress is involved in LLLT mechanism of action on skin healing in rats. *54*.

Hashmi, J. T., Huang, Y. Y., Sharma, S. K., Kurup, D. B., De Taboada, L., Carroll, J. D., & Hamblin, M. R. (2010). Effect of pulsing in low-level light therapy. *Lasers Surg Med*, *42*(6), 450-466. https://doi.org/10.1002/lsm.20950

Hawkins, D., Houreld, N., & Abrahamse, H. (2005). Low level laser therapy (LLLT) as an effective therapeutic modality for delayed wound healing. *Ann N Y Acad Sci*, *1056*, 486-493. https://doi.org/10.1196/annals.1352.040

Hayashi, H., & Sakai, T. (2011). Animal models for the study of liver fibrosis: new insights from knockout mouse models. *Am J Physiol Gastrointest Liver Physiol*, *300*(5), G729-738. https://doi.org/10.1152/ajpgi.00013.2011

Heindryckx, F., Colle, I., & Van Vlierberghe, H. J. I. j. o. e. p. (2009). Experimental mouse models for hepatocellular carcinoma research. *90*(4), 367-386.

Huang, Y. Y., Chen, A. C., Carroll, J. D., & Hamblin, M. R. (2009). Biphasic dose response in low level light therapy. *Dose Response*, *7*(4), 358-383. https://doi.org/10.2203/dose-response.09-027.Hamblin

Huang, Y. Y., Nagata, K., Tedford, C. E., McCarthy, T., & Hamblin, M. R. (2013). Low-level laser therapy (LLLT) reduces oxidative stress in primary cortical neurons in vitro. *J Biophotonics*, *6*(10), 829-838. https://doi.org/10.1002/jbio.201200157

Ichimura, M., Kawase, M., Masuzumi, M., Sakaki, M., Nagata, Y., Tanaka, K., Suruga, K., Tamaru, S., Kato, S., Tsuneyama, K., & Omagari, K. (2015). High-fat and high-cholesterol diet rapidly induces non-alcoholic steatohepatitis with advanced fibrosis in Sprague-Dawley rats. *Hepatol Res*, *45*(4), 458-469. https://doi.org/10.1111/hepr.12358

Iredale, J. P. (2001). Hepatic stellate cell behavior during resolution of liver injury. *Semin Liver Dis*, *21*(3), 427-436. https://doi.org/10.1055/s-2001-17557

Ishak, K., Baptista, A., Bianchi, L., Callea, F., De Groote, J., Gudat, F., Denk, H., Desmet, V., Korb, G., MacSween, R. N., & et al. (1995). Histological grading and staging of chronic hepatitis. *J Hepatol*, *22*(6), 696-699. https://doi.org/10.1016/0168-8278(95)80226-6

Itagaki, H., Shimizu, K., Morikawa, S., Ogawa, K., & Ezaki, T. (2013). Morphological and functional characterization of non-alcoholic fatty liver disease induced by a methionine-choline-deficient diet in C57BL/6 mice. *Int J Clin Exp Pathol*, *6*(12), 2683-2696. https://www.ncbi.nlm.nih.gov/pubmed/24294355

Ito, M., Suzuki, J., Tsujioka, S., Sasaki, M., Gomori, A., Shirakura, T., Hirose, H., Ito, M., Ishihara, A., Iwaasa, H., & Kanatani, A. (2007). Longitudinal analysis of murine steatohepatitis model induced by chronic exposure to high-fat diet. *Hepatol Res*, *37*(1), 50-57. https://doi.org/10.1111/j.1872-034X.2007.00008.x

Itoh, K., Tong, K. I., & Yamamoto, M. (2004). Molecular mechanism activating Nrf2-Keap1 pathway in regulation of adaptive response to electrophiles. *Free Radic Biol Med*, *36*(10), 1208-1213. https://doi.org/10.1016/j.freeradbiomed.2004.02.075

Iwaisako, K., Jiang, C., Zhang, M., Cong, M., Moore-Morris, T. J., Park, T. J., Liu, X., Xu, J., Wang, P., Paik, Y. H., Meng, F., Asagiri, M., Murray, L. A., Hofmann, A. F., Iida, T., Glass, C. K., Brenner, D. A., & Kisseleva, T. (2014). Origin of myofibroblasts in the fibrotic liver in mice. *Proc Natl Acad Sci U S A*, *111*(32), E3297-3305. https://doi.org/10.1073/pnas.1400062111

Jang, J., Kang, K., Kim, Y., Kang, Y., & Lee, I. (2008). Reevaluation of experimental model of hepatic fibrosis induced by hepatotoxic drugs: an easy, applicable, and reproducible model. Transplantation proceedings,

Jia, J. D., Bauer, M., Cho, J. J., Ruehl, M., Milani, S., Boigk, G., Riecken, E. O., & Schuppan, D. (2001). Antifibrotic effect of silymarin in rat secondary biliary fibrosis is mediated by downregulation of procollagen alpha1(I)

and TIMP-1. *J Hepatol*, *35*(3), 392-398. https://doi.org/10.1016/s0168-8278(01)00148-9

Jin, N., Deng, J., Chadashvili, T., Zhang, Y., Guo, Y., Zhang, Z., Yang, G.-Y., Omary, R. A., & Larson, A. C. J. R. (2010). Carbogen Gas–Challenge BOLD MR Imaging in a Rat Model of Diethylnitrosamine-induced Liver Fibrosis. *254*(1), 129-137.

Jówko, E., Płaszewski, M., Cieśliński, M., Sacewicz, T., Cieśliński, I., Jarocka, M. J. B. S. S., Medicine, & Rehabilitation. (2019). The effect of low level laser irradiation on oxidative stress, muscle damage and function following neuromuscular electrical stimulation. A double blind, randomised, crossover trial. *11*(1), 1-14.

Kaplan, M. M., Cheng, S., Price, L. L., & Bonis, P. A. (2004). A randomized controlled trial of colchicine plus ursodiol versus methotrexate plus ursodiol in primary biliary cirrhosis: ten-year results. *Hepatology*, *39*(4), 915-923. https://doi.org/10.1002/hep.20103

Karu, T. (1989). Photobiology of low-power laser effects. *Health Phys*, *56*(5), 691-704. https://doi.org/10.1097/00004032-198905000-00015

Karu, T. (2010). Mitochondrial mechanisms of photobiomodulation in context of new data about multiple roles of ATP. *Photomed Laser Surg*, *28*(2), 159-160. https://doi.org/10.1089/pho.2010.2789

Khadrawy, S. M., Mohamed, H. M., Mahmoud, A. M. J. E. S., & Research, P. (2021). Mesenchymal stem cells ameliorate oxidative stress, inflammation, and hepatic fibrosis via Nrf2/HO-1 signaling pathway in rats. *28*(2), 2019-2030.

Kim, K. Y., Rhim, T., Choi, I., & Kim, S. S. (2001). N-acetylcysteine induces cell cycle arrest in hepatic stellate cells through its reducing activity. *J Biol Chem*, *276*(44), 40591-40598. https://doi.org/10.1074/jbc.M100975200

Knodell, R. G., Ishak, K. G., Black, W. C., Chen, T. S., Craig, R., Kaplowitz, N., Kiernan, T. W., & Wollman, J. (1981). Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology*, *1*(5), 431-435. https://doi.org/10.1002/hep.1840010511

Kobayashi, M., & Yamamoto, M. (2005). Molecular mechanisms activating the Nrf2-Keap1 pathway of antioxidant gene regulation. *Antioxid Redox Signal*, *7*(3-4), 385-394. https://doi.org/10.1089/ars.2005.7.385

Kondou, H., Mushiake, S., Etani, Y., Miyoshi, Y., Michigami, T., & Ozono, K. (2003). A blocking peptide for transforming growth factor-beta1 activation prevents hepatic fibrosis in vivo. *J Hepatol*, *39*(5), 742-748. https://doi.org/10.1016/s0168-8278(03)00377-5

Larter, C. Z., & Yeh, M. M. (2008). Animal models of NASH: getting both pathology and metabolic context right. *J Gastroenterol Hepatol*, *23*(11), 1635-1648. https://doi.org/10.1111/j.1440-1746.2008.05543.x

Li, C., Luo, J., Li, L., Cheng, M., Huang, N., Liu, J., & Waalkes, M. P. (2003). The collagenolytic effects of the traditional Chinese medicine preparation, Han-Dan-Gan-Le, contribute to reversal of chemical-induced liver fibrosis in rats. *Life Sci*, *72*(14), 1563-1571. https://doi.org/10.1016/s0024-3205(02)02448-7

Li, D., & Friedman, S. L. (1999). Liver fibrogenesis and the role of hepatic stellate cells: new insights and prospects for therapy. *J Gastroenterol Hepatol*, *14*(7), 618-633. https://doi.org/10.1046/j.1440-1746.1999.01928.x

Lieber, C. S. (1997). Ethanol metabolism, cirrhosis and alcoholism. *Clin Chim Acta*, *257*(1), 59-84. https://doi.org/10.1016/s0009-8981(96)06434-0

Lieber, C. S., Weiss, D. G., Groszmann, R., Paronetto, F., Schenker, S., & Veterans Affairs Cooperative Study, G. (2003). II. Veterans Affairs Cooperative Study of polyenylphosphatidylcholine in alcoholic liver disease. *Alcohol Clin Exp Res*, *27*(11), 1765-1772. https://doi.org/10.1097/01.ALC.0000093743.03049.80

Liedtke, C., Luedde, T., Sauerbruch, T., Scholten, D., Streetz, K., Tacke, F., Tolba, R., Trautwein, C., Trebicka, J., Weiskirchen, R. J. F., & repair, t. (2013). Experimental liver fibrosis research: update on animal models, legal issues and translational aspects. *6*(1), 1-25.

Locke, G. R., 3rd, Therneau, T. M., Ludwig, J., Dickson, E. R., & Lindor, K. D. (1996). Time course of histological progression in primary biliary cirrhosis. *Hepatology*, *23*(1), 52-56. https://doi.org/10.1002/hep.510230108

Luedde, T., Schwabe, R. F. J. N. r. G., & hepatology. (2011). NF-κB in the liver—linking injury, fibrosis and hepatocellular carcinoma. *8*(2), 108-118.

Mahmoud, A. M., Mohammed, H. M., Khadrawy, S. M., & Galaly, S. R. J. C.-B. I. (2017). Hesperidin protects against chemically induced hepatocarcinogenesis via modulation of Nrf2/ARE/HO-1, PPARγ and TGF-β1/Smad3 signaling, and amelioration of oxidative stress and inflammation. *277*, 146-158.

Mancini, R., Benedetti, A., & Jezequel, A. M. (1994). An interleukin-1 receptor antagonist decreases fibrosis induced by dimethylnitrosamine in rat liver. *Virchows Arch*, *424*(1), 25-31. https://doi.org/10.1007/BF00197389

Masha, R. T., Houreld, N. N., Abrahamse, H. J. P., & surgery, l. (2013). Low-intensity laser irradiation at 660 nm stimulates transcription of genes involved in the electron transport chain. *31*(2), 47-53.

Mathurin, P., Duchatelle, V., Ramond, M. J., Degott, C., Bedossa, P., Erlinger, S., Benhamou, J. P., Chaput, J. C., Rueff, B., & Poynard, T. (1996). Survival and prognostic factors in patients with severe alcoholic hepatitis treated with prednisolone. *Gastroenterology*, *110*(6), 1847-1853. https://doi.org/10.1053/gast.1996.v110.pm8964410

Mato, J. M., Camara, J., Fernandez de Paz, J., Caballeria, L., Coll, S., Caballero, A., Garcia-Buey, L., Beltran, J., Benita, V., Caballeria, J., Sola, R., Moreno-Otero, R., Barrao, F., Martin-Duce, A., Correa, J. A., Pares, A., Barrao, E., Garcia-Magaz, I., Puerta, J. L., . . . Rodes, J. (1999). S-adenosylmethionine in alcoholic liver cirrhosis: a randomized, placebo-controlled, double-blind, multicenter clinical trial. *J Hepatol*, *30*(6), 1081-1089. https://doi.org/10.1016/s0168-8278(99)80263-3

McMahon, M., Itoh, K., Yamamoto, M., & Hayes, J. D. (2003). Keap1-dependent proteasomal degradation of transcription factor Nrf2 contributes to the negative regulation of antioxidant response element-driven gene expression. *J Biol Chem*, *278*(24), 21592-21600. https://doi.org/10.1074/jbc.M300931200

Melhem, M. F., Rao, K., Kunz, H. W., Kazanecki, M., & Gill, T. J. J. C. r. (1989). Genetic control of susceptibility to diethylnitrosamine carcinogenesis in inbred ACP (grc+) and R16 (grc) rats. *49*(23), 6813-6821.

Melon, L. C., Wray, K. N., Moore, E. M., & Boehm, S. L., 2nd. (2013). Sex and age differences in heavy binge drinking and its effects on alcohol responsivity following abstinence. *Pharmacol Biochem Behav*, *104*, 177-187. https://doi.org/10.1016/j.pbb.2013.01.005

Mester, E. (1966). [The use of the laser beam in therapy]. *Orv Hetil*, *107*(22), 1012-1016. https://www.ncbi.nlm.nih.gov/pubmed/5935784 (A laser sugar alkalmazasa a gyogyaszatban.)

Miyoshi, H., Rust, C., Roberts, P. J., Burgart, L. J., & Gores, G. J. (1999). Hepatocyte apoptosis after bile duct ligation in the mouse involves Fas. *Gastroenterology*, *117*(3), 669-677. https://doi.org/10.1016/s0016-5085(99)70461-0

Morgan, T. R., Weiss, D. G., Nemchausky, B., Schiff, E. R., Anand, B., Simon, F., Kidao, J., Cecil, B., Mendenhall, C. L., Nelson, D., Lieber, C., Pedrosa, M., Jeffers, L., Bloor, J., Lumeng, L., Marsano, L., McClain, C., Mishra, G., Myers, B., . . . Sather, M. R. (2005). Colchicine treatment of alcoholic cirrhosis: a randomized, placebo-controlled clinical trial of patient survival. *Gastroenterology*, *128*(4), 882-890. https://doi.org/10.1053/j.gastro.2005.01.057

Morita, S. Y., Tsuda, T., Horikami, M., Teraoka, R., Kitagawa, S., & Terada, T. (2013). Bile salt-stimulated phospholipid efflux mediated by ABCB4 localized in nonraft membranes. *J Lipid Res*, *54*(5), 1221-1230. https://doi.org/10.1194/jlr.M032425

Moriyama, Y., Moriyama, E. H., Blackmore, K., Akens, M. K., Lilge, L. J. P., & Photobiology. (2005). In vivo study of the inflammatory modulating effects of low-level laser therapy on iNOS expression using bioluminescence imaging. *81*(6), 1351-1355.

Nakae, D., Yoshiji, H., Mizumoto, Y., Horiguchi, K., Shiraiwa, K., Tamura, K., Denda, A., & Konishi, Y. (1992). High incidence of hepatocellular carcinomas induced by a choline deficient L-amino acid defined diet in rats. *Cancer Res*, *52*(18), 5042-5045. https://www.ncbi.nlm.nih.gov/pubmed/1516060

Oakley, F., Meso, M., Iredale, J. P., Green, K., Marek, C. J., Zhou, X., May, M. J., Millward-Sadler, H., Wright, M. C., & Mann, D. A. (2005). Inhibition of inhibitor of kappaB kinases stimulates hepatic stellate cell apoptosis and accelerated recovery from rat liver fibrosis. *Gastroenterology*, *128*(1), 108-120. https://doi.org/10.1053/j.gastro.2004.10.003

Oh, S.-W., Kim, D.-H., Ha, J.-R., Kim, D.-Y. J. B., & Bulletin, P. (2009). Anti-fibrotic effects of a methylenedioxybenzene compound, CW209292 on dimethylnitrosamine-induced hepatic fibrosis in rats. *32*(8), 1364-1370.

Oliveira-Junior, M. C., Monteiro, A. S., Leal-Junior, E. C., Munin, E., Osorio, R. A., Ribeiro, W., & Vieira, R. P. (2013). Low-level laser therapy ameliorates CCl4-induced liver cirrhosis in rats. *Photochem Photobiol*, *89*(1), 173-178. https://doi.org/10.1111/j.1751-1097.2012.01211.x

Orozco-Solis, R., Ramadori, G., Coppari, R., & Sassone-Corsi, P. J. E. (2015). SIRT1 relays nutritional inputs to the circadian clock through the Sf1 neurons of the ventromedial hypothalamus. *156*(6), 2174-2184.

Ozaki, I., Zhao, G., Mizuta, T., Ogawa, Y., Hara, T., Kajihara, S., Hisatomi, A., Sakai, T., & Yamamoto, K. (2002). Hepatocyte growth factor induces collagenase (matrix metalloproteinase-1) via the transcription factor Ets-1 in human hepatic stellate cell line. *J Hepatol*, *36*(2), 169-178. https://doi.org/10.1016/s0168-8278(01)00245-8

Pan, X., Ma, X., Jiang, Y., Wen, J., Yang, L., Chen, D., Cao, X., & Peng, C. (2020). A Comprehensive Review of Natural Products against Liver Fibrosis: Flavonoids, Quinones, Lignans, Phenols, and Acids. *Evid Based Complement Alternat Med*, *2020*, 7171498. https://doi.org/10.1155/2020/7171498

Park, K. C., Park, J. H., Jeon, J. Y., Kim, S. Y., Kim, J. M., Lim, C. Y., Lee, T. H., Kim, H. K., Lee, H. G., Kim, S. M., Kwon, H. J., Suh, J. S., Kim, S. W., & Choi, S. H. (2014). A new histone deacetylase inhibitor improves liver fibrosis in BDL rats through suppression of hepatic stellate cells. *Br J Pharmacol*, *171*(21), 4820-4830. https://doi.org/10.1111/bph.12590

Pirat, A., Ozgur, S., Torgay, A., Candan, S., Zeyneloglu, P., & Arslan, G. (2004). Risk factors for postoperative respiratory complications in adult liver

transplant recipients. *Transplant Proc*, *36*(1), 218-220. https://doi.org/10.1016/j.transproceed.2003.11.026

Posten, W., Wrone, D. A., Dover, J. S., Arndt, K. A., Silapunt, S., & Alam, M. (2005). Low-level laser therapy for wound healing: mechanism and efficacy. *Dermatol Surg*, *31*(3), 334-340. https://doi.org/10.1111/j.1524-4725.2005.31086

Ramos-Tovar, E., & Muriel, P. (2020). Molecular Mechanisms That Link Oxidative Stress, Inflammation, and Fibrosis in the Liver. *Antioxidants (Basel)*, *9*(12). https://doi.org/10.3390/antiox9121279

Rinella, M. E., & Green, R. M. J. J. o. h. (2004). The methionine-choline deficient dietary model of steatohepatitis does not exhibit insulin resistance. *40*(1), 47-51.

Rodriguez-Garay, E. A., Aguero, R. M., Pisani, G., Trbojevich, R. A., Farroni, A., & Viglianco, R. A. (1996). Rat model of mild stenosis of the common bile duct. *Res Exp Med (Berl)*, *196*(2), 105-116. https://doi.org/10.1007/BF02576832

Roehlen, N., Crouchet, E., & Baumert, T. F. (2020). Liver Fibrosis: Mechanistic Concepts and Therapeutic Perspectives. *Cells*, *9*(4). https://doi.org/10.3390/cells9040875

Ryhanen, L., Stenback, F., Ala-Kokko, L., & Savolainen, E. R. (1996). The effect of malotilate on type III and type IV collagen, laminin and fibronectin metabolism in dimethylnitrosamine-induced liver fibrosis in the rat. *J Hepatol*, *24*(2), 238-245. https://doi.org/10.1016/s0168-8278(96)80035-3

Saiman, Y., & Friedman, S. L. (2012). The role of chemokines in acute liver injury. *Front Physiol*, *3*, 213. https://doi.org/10.3389/fphys.2012.00213

Sánchez-Pérez, Y., Carrasco-Legleu, C., García-Cuellar, C., Pérez-Carreón, J., Hernández-García, S., Salcido-Neyoy, M., Alemán-Lazarini, L., & Villa-Treviño, S. J. C. l. (2005). Oxidative stress in carcinogenesis. Correlation between lipid peroxidation and induction of preneoplastic lesions in rat hepatocarcinogenesis. *217*(1), 25-32.

Scholten, D., Trebicka, J., Liedtke, C., & Weiskirchen, R. J. L. a. (2015). The carbon tetrachloride model in mice. *49*(1_suppl), 4-11.

Seki, E., & Schwabe, R. F. (2015). Hepatic inflammation and fibrosis: functional links and key pathways. *Hepatology*, *61*(3), 1066-1079. https://doi.org/10.1002/hep.27332

Sharma, A., & Nagalli, S. (2021). Chronic liver disease. In *StatPearls [Internet]*. StatPearls Publishing.

Shinohara, M., Ji, C., & Kaplowitz, N. (2010). Differences in betaine-homocysteine methyltransferase expression, endoplasmic reticulum stress response, and liver injury between alcohol-fed mice and rats. *Hepatology*, *51*(3), 796-805. https://doi.org/10.1002/hep.23391

Sies, H., & Cadenas, E. (1985). Oxidative stress: damage to intact cells and organs. *Philos Trans R Soc Lond B Biol Sci*, *311*(1152), 617-631. https://doi.org/10.1098/rstb.1985.0168

Silveira, P. C., Scheffer Dda, L., Glaser, V., Remor, A. P., Pinho, R. A., Aguiar Junior, A. S., & Latini, A. (2016). Low-level laser therapy attenuates the acute inflammatory response induced by muscle traumatic injury. *Free Radic Res*, *50*(5), 503-513. https://doi.org/10.3109/10715762.2016.1147649

Sohn, H., Ko, Y., Park, M., Kim, D., Moon, Y. L., Jeong, Y. J., Lee, H., Moon, Y., Jeong, B. C., Kim, O., & Lim, W. (2015). Effects of light-emitting diode irradiation on RANKL-induced osteoclastogenesis. *Lasers Surg Med*, *47*(9), 745-755. https://doi.org/10.1002/lsm.22413

Sun, S., Sursal, T., Adibnia, Y., Zhao, C., Zheng, Y., Li, H., Otterbein, L. E., Hauser, C. J., & Itagaki, K. J. P. o. (2013). Mitochondrial DAMPs increase endothelial permeability through neutrophil dependent and independent pathways. *8*(3), e59989.

Tan, Z., Qian, X., Jiang, R., Liu, Q., Wang, Y., Chen, C., Wang, X., Ryffel, B., & Sun, B. (2013). IL-17A plays a critical role in the pathogenesis of liver fibrosis through hepatic stellate cell activation. *J Immunol*, *191*(4), 1835-1844. https://doi.org/10.4049/jimmunol.1203013

Tosello-Trampont, A.-C., Landes, S. G., Nguyen, V., Novobrantseva, T. I., & Hahn, Y. S. J. J. o. B. C. (2012). Kuppfer cells trigger nonalcoholic steatohepatitis development in diet-induced mouse model through tumor necrosis factor-α production. *287*(48), 40161-40172.

Trotter, L. A., Patel, D., Dubin, S., Guerra, C., McCloud, V., Lockwood, P., Messer, R., Wataha, J. C., & Lewis, J. B. (2017). Violet/blue light activates Nrf2 signaling and modulates the inflammatory response of THP-1 monocytes. *Photochem Photobiol Sci*, *16*(6), 883-889. https://doi.org/10.1039/c6pp00299d

Uyama, N., Shimahara, Y., Okuyama, H., Kawada, N., Kamo, S., Ikeda, K., & Yamaoka, Y. (2003). Carbenoxolone inhibits DNA synthesis and collagen gene expression in rat hepatic stellate cells in culture. *J Hepatol*, *39*(5), 749-755. https://doi.org/10.1016/s0168-8278(03)00375-1

Van de Casteele, M., Roskams, T., Van der Elst, I., van Pelt, J. F., Fevery, J., & Nevens, F. (2004). Halofuginone can worsen liver fibrosis in bile duct obstructed rats. *Liver Int*, *24*(5), 502-509. https://doi.org/10.1111/j.1478-3231.2004.0950.x

Wallace, M., Hamesch, K., Lunova, M., Kim, Y., Weiskirchen, R., Strnad, P., & Friedman, S. J. L. a. (2015). Standard operating procedures in experimental liver research: thioacetamide model in mice and rats. *49*(1_suppl), 21-29.

Wang, Y. Q., Ikeda, K., Ikebe, T., Hirakawa, K., Sowa, M., Nakatani, K., Kawada, N., & Kaneda, K. (2000). Inhibition of hepatic stellate cell proliferation and activation by the semisynthetic analogue of fumagillin TNP-470 in rats. *Hepatology*, *32*(5), 980-989. https://doi.org/10.1053/jhep.2000.18658

Watanabe, M., Uchida, Y., Sato, S., Moritani, M., Hamamoto, S., Mishiro, T., Akagi, S., Kinoshita, Y., & Kohge, N. (2001). Report of a case showing a recovery from liver cirrhosis to chronic hepatitis, type C, after glycyrrhizin injection for 2 years and a sustained response by the following interferon therapy. *Am J Gastroenterol*, *96*(6), 1947-1949. https://doi.org/10.1111/j.1572-0241.2001.03912.x

Weber, L. W., Boll, M., & Stampfl, A. (2003). Hepatotoxicity and mechanism of action of haloalkanes: carbon tetrachloride as a toxicological model. *Crit Rev Toxicol*, *33*(2), 105-136. https://doi.org/10.1080/713611034

Weiskirchen, R., & Tacke, F. (2014). Cellular and molecular functions of hepatic stellate cells in inflammatory responses and liver immunology.

Hepatobiliary Surg Nutr, *3*(6), 344-363. https://doi.org/10.3978/j.issn.2304-3881.2014.11.03

Wilkinson, A. L., Qurashi, M., & Shetty, S. (2020). The Role of Sinusoidal Endothelial Cells in the Axis of Inflammation and Cancer Within the Liver. *Front Physiol*, *11*, 990. https://doi.org/10.3389/fphys.2020.00990

Xie, G., Wang, X., Wang, L., Wang, L., Atkinson, R. D., Kanel, G. C., Gaarde, W. A., & Deleve, L. D. (2012). Role of differentiation of liver sinusoidal endothelial cells in progression and regression of hepatic fibrosis in rats. *Gastroenterology*, *142*(4), 918-927 e916. https://doi.org/10.1053/j.gastro.2011.12.017

Yang, M., & Zhang, C. (2021). The role of liver sinusoidal endothelial cells in cancer liver metastasis. *Am J Cancer Res*, *11*(5), 1845-1860. https://www.ncbi.nlm.nih.gov/pubmed/34094657

Ying, H. Z., Chen, Q., Zhang, W. Y., Zhang, H. H., Ma, Y., Zhang, S. Z., Fang, J., & Yu, C. H. (2017). PDGF signaling pathway in hepatic fibrosis pathogenesis and therapeutics (Review). *Mol Med Rep*, *16*(6), 7879-7889. https://doi.org/10.3892/mmr.2017.7641

Yu, H. S., Wu, C. S., Yu, C. L., Kao, Y. H., & Chiou, M. H. (2003). Helium-neon laser irradiation stimulates migration and proliferation in melanocytes and induces repigmentation in segmental-type vitiligo. *J Invest Dermatol*, *120*(1), 56-64. https://doi.org/10.1046/j.1523-1747.2003.12011.x