KUPFFER CELL: PATHO-PHYSIOLOGICAL ASPECT IN CHRONIC ALCOHOL LIVER DISEASE

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ABSTRACT

Alcoholic liver injury involves a complex array of derangements in cellular signalling of hepatic parenchymal and non-parenchymal cells as well as cells of the immune system. Here, we review the literature on the role of one of the non parenchymal cell i.e Kupffer Cells of the liver in the pathogenesis of alcoholic liver disease. In the hepatocyte, chronic ethanol abuse leads to lipid accumulation and liver steatosis. Multiple pathways are affected to promote lipid accumulation in the ethanol-exposed hepatocyte. Chronic ethanol renders Kupffer cells hyper-responsive to endotoxin, which results in production of inflammatory cytokines and the tumor necrosis factor-α (TNF α) via a Toll-like receptor 4 dependent pathway, leading to inflammation and hepatic necrosis. Dysfunction of the innate and adaptive immune responses caused by ethanol contributes to impaired anti-viral response, inflammatory injury, and autoimmune activation. Recent developments in the literature are reviewed, and we suggest Kupffer cell’s responses due to influence of alcohol are interwoven the path physiological mechanisms of liver injury in Chronic alcohol liver disease (CALD).

KEY WORDS: Chronic alcohol liver disease (CALD), Tumour necrosis factor-α (TNF α), Kupffer Cells, endotoxin.
INTRODUCTION

1.1 The Liver

The liver is the largest solid organ, the largest gland, and the main metabolic organ of the body. The liver is the first site of passage for venous blood arriving from the intestines via vena porta. The area around the influx blood vessels is named peripoortal. The areas surrounding efflux blood vessels are the perivenous. The perportal areas highly complex and consists of dense matrix containing collagen where afferent blood vessels are found, together with bile ducts, nerves and lymph. Spaces within the matrix contain a variable cell population, such as fibroblasts, hematopoietic cells and inflammatory cells. Also found here are epithelial cells of the bile ducts, endothelial cells of the blood vessels, and smooth muscle of arteries and veins. [1]

The liver lobule consists mainly of plates of hepatocytes and sinusoids, with a light matrix of collagen to form a network between the two. Kupffer cells, as well as fat storing stellate cells are found here. These types of cells reside mainly in the tissue space between the hepatocyte and the sinusoids. Terminal bile ductules connect here to the bile cannaliculi between hepatocytic plates. [2,3] The walls of the hepatic sinusoid are lined by three different cell types: the sinusoidal endothelial cell, Kupffer cells, and stellate cells. Addaitionally, pit cells, the liver specific NK T cells are often present in the sinusoidal lumen. [2]

![Figure 1: schematic drawing of a liver lobule, the functional unit of the liver, with its periportal and perivenous regions.](image)[3]
1.1 Liver cell types

There are five different cell types in the liver which occupy about 80% of the hepatic volume. The remaining 20% of the hepatic volume comprises the extracellular space and extracellular matrix.

i. Hepatocyte

ii. Endothelial cells

iii. Stellate cells (Ito cells), the liver fat storing cells

iv. Kupffer cells, which are the liver resident macrophages

Among these liver cells, hepatocytes are the largest in size and the most abundant as they occupy close to 50 to 60% of the total liver volume and account for two-thirds of total liver cells. The other four cell types are referred to as non-parenchymal or liver sinusoidal cells. Non-parenchymal cells comprise 30-40 % of the total cell number and 1500 of the volume of the liver. Of these, approximately one-third is Kupffer cells, one-third endothelial cells and one-third fat-storing cells. [4]

They are smaller in size and lesser in number than the parenchymal cells. Beside these, there are many other smaller populations of cells, some of which will be dealt with more closely related to immune cells in the liver, like natural killer (NK) cells and dendritic cells. Other cell types include bile duct cells, smooth muscle cells and various blood cells.

1.1.1 Hepatocytes

Hepatocytes are large, and rich in organelles such as endoplasmatic reticulum and Golgi apparatuses. The typical hepatocyte is cubical with sides of 20-30 µm. The typical volume of a hepatocyte is $3.4 \times 10^{-9}$ cm$^3$. Smooth endoplasmic reticulum is abundant in hepatocytes, whereas most cells in the body have only small amounts. [5] They contain many and large mitochondria, as well as lysomes and peroxisomes. A main function of hepatocytes is to participate in lipid, carbohydrate and protein metabolism. Structure and function of the hepatocytes within the liver lobule differs greatly depending on proximity to periportal or perivenous areas. Periportal type hepatocytes are often smaller, but, have larger mitochondria, and a larger Golgi apparatus as compared to the perivenous type. Perivenous hepatocytes on the other hand have larger in endoplasmatic reticulum. Functionally, periportal hepatocytes are more involved in gluconeogenesis, while perivenous are involved
in glycolysis. Additionally, perivenous hepatocytes are dominant with respect to P450-dependent hydroxylation reactions, and glutamine synthetase.

1.1.2 Endothelial cells

A liver sinusoid is a type of sinusoidal blood vessel (with fenestrated, discontinuous endothelium) that serves as a location for the oxygen-rich blood from the hepatic artery and the nutrient-rich blood from the portal vein. Liver sinusoidal endothelial cells (LSECs) have long been noted to contribute to liver regeneration after liver injury. In normal liver, the major cellular source of HGF is the hepatic stellate cell, but after liver injury, HGF expression has been thought to increase markedly in proliferating LSECs.

The sinusoidal endothelial cells line the walls of the hepatic sinusoid and perform a function of filtration due to the presence of fenestrate. These cells also demonstrate large endocytic capacity for extracellular matrix components and immune complexes. In general they engulf smaller size particles, and may play a role in clearance of viruses, but do not possess phagocytic function as antigen presenting cells and secrete certain cytokines and eicosanoids.

1.1.3 Stellate cells

Hepatic stellate cells (here HSC), also known as perisinusoidal cells or Ito cells (earlier lipocytes or fat-storing cells), are pericytes found in the perisinusoidal space (a small area between the sinusoids and hepatocytes) of the liver also known as the space of Disse. The liver plays a central role in uptake and storage of vitamin A (retinol), and stores about 95% of retinoids found in the body. The fat storing perisinusoidal cells of the liver, stellate cells are the main vitamin A storing cells. They harbour large amounts of retinol and retinyl palmitate in lipid droplets within their cell cytoplasm. They are located in the space of Disse (between hepatocytes and sinusoid) and generally protrude to come into contact with several sinusoids.

Additionally, they function to control the turnover of extracellular matrix and regulate sinusoids contractility. The stellate cells may become activated under stressful conditions and transform into myofibroblast-like cells which play a key role in inflammatory fibrotic response. When activated, stellate cells not only proliferate, but also produce increased amount of extracellular matrix per cell. Transforming growth factor beta (TGFB) is one of the most important signals to activate stellate cells, which leads to a higher transcriptional rate.
of mRNAs coding for extracellular matrix components such as collagen I, fibronectin and proteoglycans. Lipid peroxidation products are also an important stimulus, whose effect may be augmented in oxidative stress conditions.

1.1.4 Kupffer cells (KC)

The liver harbours large amounts of kupffer cells (KC), which represent the largest tissue resident macrophage population of the body. Kupffer cells are liver-specific macrophages which were first identified in the liver by von Kupffer (1876).

Kupffer cells belong to a class of immune cells called macrophages, which are found throughout most tissues. Macrophages take various actions to eliminate foreign materials (e.g., bacteria or bacterial products) from the body. For example, macrophages can ingest and destroy foreign materials or secrete immune molecules as well as molecules that regulate the functions of other cells involved in the immune response. These regulatory molecules are called cytokines.[11]

1.2.4.1 Structure of KC

Kupffer cells are amoeboid in shape and adhere to the surface of fenestrated sinusoidal endothelial cells. Their development begins in the bone marrow with the genesis of promonocytes and monoblasts into monocytes, and then on to peripheral blood monocytes, completing their differentiation into Kupffer cells.[12]

In the cytosol of KC, there are a number of dense bodies and electron-lucent vacuoles of various sizes including lysosomes. Golgi apparatus, coated vesicles, pinocytic vesicles, ribosomes, centrioles, microfilaments, and microtubules are also present in the cytosol. The cytoplasm contains phagocytic vesicles, which in turn can contain cellular fragments and haemosiderin coming from phagocytosis and destruction of old erythrocytes. A notable feature of Kupffer cells are worm-like tubules located in their cytoplasm probably representing reservoirs of cell membrane available for rapid phagocytic response to particulate matter. Although all macrophages are ultimately derived from the stem cells of the bone marrow, KC can also propagate in the liver sinusoids.

1.2.4.2 Location of Kupffer Cell in Liver

The majority of Kupffer cells are found in the liver periportal regions either in the gaps between adjacent sinusoidal endothelial cells or on their surface. [13] They are located within
the sinusoid and are in constant contact with gut-derived particles that lead to low but constant amount of activation of these monocytes derived cells.

1.2.4.3 Enzymes Acquaintances with Kupffer Cell

Kupffer cells display high glucose-6-phosphate dehydrogenase (G6PDH) activity,\textsuperscript{[14]} which plays an important role in the metabolic response to phagocytosis. A key enzyme present in KC is NADPH oxidase which plays a decisive role in the development of alcohol-induced liver injury.\textsuperscript{[15]} The cytochrome P450 enzymes, and concretely P450 2E1 (CYP2E1), are also expressed in Kupffer cells. In addition, several glutathione- S-transferase (GST) isoenzymes and glutathione peroxidase may enable the KC to detoxify potentially hepatotoxic substances.\textsuperscript{[16–18]}

1.2.4.4 Function of kupffer cells

Kupffer cells have many specific functions that are essential for the preservation of homeostasis in the liver under several conditions. Like other macrophages, KCs are involved in both the innate and acquired immunity. The primary functions of Kupffer cells are phagocytosis, processing of ingested material, antigen presentation and secretion of biologically active products.\textsuperscript{[18]} For these purposes they contain receptors on their surface and binding sites in the cytosol for specific ligands of phagocytosable particles and for many soluble substances (Table 1).

Table 1: Various substances released during activation of kupffer cells.\textsuperscript{[19, 20]}

<table>
<thead>
<tr>
<th>Ligands</th>
<th>Activators</th>
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<tbody>
<tr>
<td>Fc part of immunoglobulins</td>
<td>IFN-(\gamma) (macrophages- activating factor)</td>
</tr>
<tr>
<td>Mannose/ N-acetylglucosamine</td>
<td>LPS (endotoxin)</td>
</tr>
<tr>
<td>Fucose</td>
<td>TNF-(\alpha) (cachectin)</td>
</tr>
<tr>
<td>Galactose/ N-acetylgalactosamine</td>
<td>Virus (Sendai, Newcastle disease)</td>
</tr>
<tr>
<td>Platelet- activating factor</td>
<td>Platelet- activating factor</td>
</tr>
<tr>
<td>Apolipoprotein C (high density lipoproteins)</td>
<td>Muramyl dipeptide</td>
</tr>
<tr>
<td>Scavenger receptor for modified lipoproteins</td>
<td>Nucleotide triphosphates and diphosphates</td>
</tr>
<tr>
<td>Compliment</td>
<td>PMA</td>
</tr>
<tr>
<td>Cytokines: IL-1,-4,-6,-10,INF, TNF, TNF-(\beta)</td>
<td>Ionophores ((H^+) and (Ca^{2+}))</td>
</tr>
<tr>
<td>Hormones: insulin, prostaglandins</td>
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1.2.4.5 Secretary products/ mediators of Kupffer cells

Kupffer cells are involved in the pathogenesis of liver injury mediated by chemical substances, toxins and pharmacological agents\textsuperscript{[21, 22]} such as carbontetrachloride (CCl\textsubscript{4}),\textsuperscript{[23]} endotoxin,\textsuperscript{[24]} galactosamine \textsuperscript{[25]} and acetaminophen \textsuperscript{[26]} through the release of biologically active substances that promote the pathogenic process.\textsuperscript{[27]} In liver injury and hepatocellular necrosis activated Kupffer cells are a major source of inflammatory mediators including; cytokines, superoxide, nitric oxide, eicosanoids, chemokines, lysosomal and proteolytic enzymes and demonstrate increased cytotoxicity and chemotaxis.\textsuperscript{[26]}

Activated Kupffer cells produce several groups of biologically active substances (Table 2), which confer many functions including clearance and destruction of bacteria, yeast, parasites, endotoxins, tumour cells and particular cell debris, defence against viruses, modulation of immune and inflammatory responses, tissue and matrix remodelling, control of hepatocyte functions, metabolism of iron and bilirubin, and regulation of haematopoiesis and clotting.

Specific ligand-receptor interaction may be transduced to the site of realization in some cases by GTP binding proteins. These proteins activate phospholipase C(D\textsuperscript{9})\textsuperscript{[27]} and adenylate cyclise.\textsuperscript{[20]} Phospholipase C hydrolyzes phosphatidylinositol to inositol-1,4,5-triphosphate (InsP\textsubscript{3}) and diacylglycerol. The former can mediate calcium ion mobilization from the endoplasmic reticulum while the latter activates cytosolic protein kinase C (PKC) with translocation to the membrane\textsuperscript{9}. PKC is involved in the activation of the Na\textsuperscript{+}/H\textsuperscript{+} antiporter and the NADPH oxidase leading to oxidative burst whereas Ca\textsuperscript{2+} influx is necessary for phospholipase A activation and eicosanoid synthesis. The formation of cyclic AMP leads to collagenase synthesis and release by KC,\textsuperscript{[20]} and to activation of protein kinase A and tyrosine kinase.\textsuperscript{[27]} Under some conditions, toxic and vasoactive substances also are released from Kupffer cells which are thought to play a role in a variety of liver diseases. Many of these activities may be modulated by the levels of gut derived endotoxin normally present in the portal blood.
Table 2: Biologically active substances produced by Kupffer cells.

<table>
<thead>
<tr>
<th>1. Cytokines</th>
<th>TNF-α, TGF-β, TGF-β3, IFN-γ, IFN-β2, IL-1α, IL-1β, IL-6, IL-10, CSFs, PDGF2, MIP-229</th>
</tr>
</thead>
</table>
| 2. Lipid substances  | a) Platelet-activating factor  
|                       | b) Derivatives of arachidonic acid (eicosanoids): b) prostanoids: prostacyclin, prostaglandins (D2, E2, F2), thromboxane A2  
|                       | c) Leukotrienes: 5-HETE, leukotrienes (B4, C4, D4)                                      |
| 3. Inorganic compounds| Reactive oxygen species  
|                       | Nitric oxide                                                                     |

CSF, colony-stimulating factor; PDGF, platelet-derived growth factor; MIP, macrophage-inflammatory protein; 5-HETE, 5-hydroxyeicosatetraenoic acid

1.2.4.6 Pro-inflammatory cytokines produced by Kupffer cells and modulation of their expression/activity

The main pro-inflammatory cytokines released by Kupffer cells in response to hepatocellular stress, as in table 2, stimulate hepatocytes and other nonparenchymal cells in a paracrine manner. Stimulated sinusoidal endothelial cells express cell adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and mediate immigration of neutrophils and blood monocytes supported by chemokines released by HSCs. Deteriorated hepatocytes may then be removed by mononuclear phagocytes. Various compounds may inhibit the formation of pro-inflammatory cytokines thus offering a means for modulation of the process and possibly avoiding extensive damage (inflammation) of the surrounding tissue by invading neutrophils and lymphocytes. TNF-α release from LPS-stimulated Kupffer cells requires internalization of LPS, acidification of endosomes, elevation of intracellular calcium, PKC activation, and protein tyrosine kinase activation.

1.2.4.7 Kupffer Cells and Immune Tolerance

Kupffer cells are also important in to phenomenon of immune tolerance. The interaction between lymphocytes and the resident hepatic macrophage, Kupffer cell, is relevant to the phenomenon of immune response to Ags entering the liver. Various studies have demonstrated that antigens introduced into the portal venous system fail to produce an immune response in comparison with injection into vena cave. This shows that KC are effective scavengers that they remove all immunogenic antigens before they reach the peripheral lymphoid tissue.
1.2.4.8 Oxidative burst in Kupffer cells

Reactive oxygen species (ROS) include superoxide anion (O$_2^-$), hydroxyl radical (HO), and their by-products (e.g., hydrogen peroxide H$_2$O$_2$). They do not act in specific ways through receptors or binding sites rather they exploit their chemical reactivity to any suitable compounds with which they collide. ROS are capable of causing oxidative damage to macromolecules encompassing lipid peroxidation, oxidation of amino acid side chains, formation of protein-protein cross-links, oxidation of polypeptide backbones resulting in protein fragmentation, DNA damage, and DNA strand breaks.

Thus, oxidative burst, i.e. the rapid uptake of molecular oxygen and its transformation into ROS, represents both host defence mechanisms at the site of injury and the possibility of damage for adjacent healthy tissue. It is an early event in Kupffer cell activity: increased ROS production in response to a stimulus takes place within seconds while increased production of cytokines and other factors takes several hours. Also, the respiratory burst itself, and the accompanying oxidative stress, is one of the stimuli involved in increased expression of cytokines.

1.2 THE ROLE OF KUPFFER CELLS IN LIVER DISEASES/INFECTION

Kupffer cells are involved in the defence against infections of the liver. Kupffer cells are involved in the defence against infections of the liver. Their major role in the host defence and the prognosis of liver infection is indicated by studies in experimental models of sepsis. LPS pre-treatment has been shown to increase Kupffer cell numbers leading to a reduction of bacterial load and improvement of prognosis in a Salmonella septicemia model. Impairment of the phagocytic function and the production of superoxide by Kupffer cells in models of obstructive jaundice lead to increased susceptibility to infection.

In liver disease, increase KC numbers leading to a reduction of bacterial load and improvement of prognosis and impaired KC clearance of microorganism and entotoxin from portal blood explains the observed clinical phenomena of the high incidences of gram negative septicaemia and septic shock in patients with fulminate hepatic failure and the hyperglobulinemia associated with chronic liver disease. Moreover, increased numbers of Kupffer cells in the portal tracts have been observed in patients with acute alcoholic hepatitis or chronic alcoholic liver disease.
On the other hand, production of inflammatory mediators such as IL-6, IL-12, IL-1β, TNF-α, and nitric oxide by infected KC inhibits proliferation of the microorganism. At the same time KC derived chemokines such as MIP-1α, MIP-1β, MCP-1, and MIP-2, drive monocytes and neutrophils recruitment into the liver in order to control infection. Thus, as expected; Kupffer cell inactivation results in impaired infection clearance. Being the first line of defence, Kupffer cells also represent the portal of entry for viruses such as cytomegalovirus and parasites such as *Plasmodium bergeri* and *Leishmania*, which enter and proliferate in Kupffer cells and then infect the rest of the liver cells.

1.3.1 Kupffer Cells and Chronic Alcohol liver disease

Chronic alcohol liver (CILD) disease is a chronic inflammatory disease of the liver due to chronic ethanol ingestion with the end result being alcoholic fibrosis and cirrhosis. Kupffer cells participate in this process mainly through the increased production of inflammatory mediators such as pro-inflammatory cytokines like TNF-α and IL-6, and chemokines like IL-8, MCP-1 and MIP-1α, those have been detected in patients with ALD. Many studies have shown that acute or chronic ethanol administration is associated with an increase in numbers of Kupffer cells that exhibit morphologic signs of cell activation, up regulation of CD14 expression and increased production of inflammatory mediators such as IL-1, TNF-α and oxygen free radicals.

1.3.1.1 Pathophysiology of CILD in relation to Kupffer Cells

Alcohol increases the proportion of Gram negative bacteria in the bowel flora and therefore the intra luminal production of lipopolysaccharide (LPS). Concurrently, the increase in the intestinal permeability due to alcohol-induced alterations of the epithelial barrier function results in portal vein endotoxinemia. This activates KC leading to production of inflammatory mediators, which in turn activate the endothelium and induce neutrophils and mononuclear cell recruitment and infiltration resulting in liver damage.

Furthermore, it has been suggested that alcohol may also have a direct effect on Kupffer cell activation by altering cell membrane calcium channels. Several lines of research have shown that gut–derived endotoxin plays a critical role in alcoholic liver disease. For example, studies have found that patients with alcoholic liver disease have elevated levels of endotoxin circulating in the blood. Furthermore, in experiments with rodents, researchers have found that eliminating all bacteria and, consequently, all the endotoxin from the intestine (e.g., by
using antibiotics) completely prevented alcohol–induced liver injury.[40] Similarly, by lowering the number of intestinal bacteria through other means (e.g., administration of lactobacillus bacteria, which are present in yogurt), investigators could curb the rise in endotoxin levels in alcohol–treated animals.[42]

A synergistic effect of LPS with ethanol indicates that chronic ethanol administration decreases the cellular cAMP levels of KC and this leads to enhanced NF-κB activation by LPS and TNF-α production.[43] Interestingly an increase in cAMP does not affect NF-κB activation but it decreases its transcription capability.

1.3.1.2 Endotoxin/ lipopolysaccharide (LPS): Mechanism of action in Liver injury by alcohol

Endotoxin, also known as lipopolysaccharide (LPS), represents the major by repeating polymers of oligosaccharides, is highly variable and antigenic, and is structurally unique for a given bacterial serotype. Endotoxin (LPS), one of the components of the outer wall of gram-negative bacteria, has been implicated in sepsis, organ failure, and lethal shock. Elevated levels of circulating endotoxin delivered to the liver via portal blood can cause hepatic tissue injury.[44]

![Mechanisms of alcohol-induced liver injury](image)

**Figure 1: Endotoxin: main pathway of pathogenesis of CALD**[45]

Fig 1; depicts our hypothesis that ethanol alters gut microflora, resulting in an increase in gram-negative bacteria, which is the source of endotoxin. Alternatively, ethanol could alter
the permeability of the gut to macromolecules, thus increasing the release of endotoxin from the gut into the portal circulation. When the host immune defense or liver function is impaired, endotoxins may spill over into the peripheral blood stream. Alternatively, the release of endotoxin into circulation is enhanced by proliferation of flora or when bacteria die or lyse, for example, from antibiotics. In these situations the increased production of endotoxin exceeds the clearance capacity of reticuloendothelial system.

1.3.1.3 The Effect of Alcohol on Endotoxin
The main target organ for endotoxin is the liver. Endotoxin has been shown to be a pivotal cofactor in the development of liver diseases. Alcoholics, especially those with liver disease, regularly have systemic endotoxemia. [41] After alcohol administration, blood endotoxin is elevated maximally at about 1 h. Initially, alcohol causes tolerance by mechanisms that are still not clear. After 24 h of exposure to alcohol, however, CD-14 and TNF-α are elevated six fold and threefold, respectively. [45] Interestingly, blood endotoxin is correlated with pathology (necrosis, steatosis, inflammation). During acute exposure to alcohol, carbon uptake by the perused liver due to phagocytosis of particles by Kupffer cells increases about 25%. [46] However, a recent study has reported that oxygen radical production by Kupffer cells is increased after chronic alcohol treatment.

1.4 ROLE OF OTHER FACTORS IN PATHOGENESIS OF CALD
1.4.1 Tumour Necrosis Factor-α (TNF-α)
TNF-α, which are directly cytotoxic to a variety of cell types, may be direct mediators of hepatocytes injury. A recent study has shown that rats administered ethanol eternally and injected with antibody to TNF-α is protected from ethanol-induced hepatic injury. [47] Moreover, TNF-α stimulate neutrophils migration and activation and also induce protease and oxygen radical release. Cellular infiltration of activated neutrophils, which produce oxygen radicals and secrete other toxic mediators, may increase the inflammatory response, leading to cell injury and death.

1.4.2 Kupffer Cells Play a role in Hyper metabolism induced by Ethanol
Elevation of ethanol metabolism occurs in concert with a reduction in both glycolysis and glycogen reserves due to hormone mediated depletion of hepatic carbohydrate reserves plays a role in this process, which has been named the “swift increase in alcohol metabolism” (SIAM). [48] Recently, studies have demonstrated the involvement of Kupffer cells in
carbohydrate metabolism. Thus increases in respiration and ethanol metabolism observed after ethanol treatment are blocked by inactivation of Kupffer cells. Specifically, Kupffer cells produce prostaglandins, primarily PGD2 and PGE2, which stimulate production of glucose from endogenous hepatic glycogen by activating phosphorylase A.\textsuperscript{[49]}

CONCLUSION

KCs play central role in the initiation and propagation of pathological changes occurs in ALD due to alcohol consumption. Several cytokines and chemokines released by activating KC aggravate liver leads to hepatotoxicity. KC which a macrophages; get suppressed by ethanol that potentiates endotoxin- kupffer cell mediated damage under the effect of alcohol. Moreover, Reactive oxygen species (ROS) leads to activate the mechanism of activation of KC.

However, KC also participates in protective mechanisms via the production of mediators that induce synthesis of the antioxidant agent glutathione or the production of nitric oxide. IL-10 and IL-18, cytokines secreted by activated KC, important factors of anti-inflammatory, are heptoprotective in nature. KC maintains the microenvironment, playing multiple effects on liver. The enhancement of KC protective effects in ALD treatment, reduction of damage to the liver and eventually reaching a unified effectiveness requires further research.

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