



Review

Beneficial role of bioactive lipids in the pathobiology, prevention, and management of HBV, HCV and alcoholic hepatitis, NAFLD, and liver cirrhosis: A review



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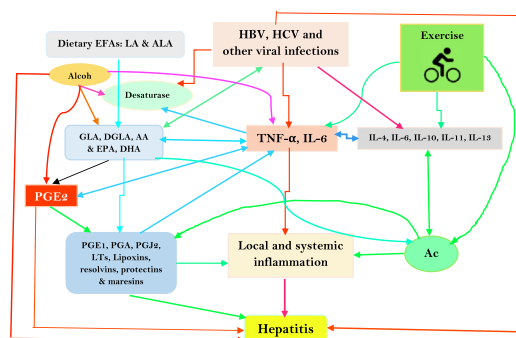
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HIGHLIGHTS

- HBV, HCV, and alcoholic and non-alcoholic fatty liver disease lead to liver cirrhosis.
- All these are inflammatory conditions with PUFA deficiency state.
- HBV, HCV, and alcohol inhibit PUFA metabolism.
- PUFAs and their metabolites have anti-viral and cytoprotective actions.
- PUFAs and vitamin C may be of benefit in NAFLD, AFLD, and liver cirrhosis.

GRAPHICAL ABSTRACT



Scheme showing possible role of HBV and HCV on cytokines, PUFA metabolism and development of hepatitis.

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ABSTRACT

It has been suggested that hepatitis B virus (HBV)- and hepatitis C virus (HCV)-induced hepatic damage and cirrhosis and associated hypoalbuminemia, non-alcoholic fatty liver disease (NAFLD), and alcoholic fatty liver disease (AFLD) are due to an imbalance between pro-inflammatory and anti-inflammatory bioactive lipids. Increased tumour necrosis factor (TNF)- α production induced by HBV and HCV leads to a polyunsaturated fatty acid (PUFA) deficiency and hypoalbuminemia. Albumin mobilizes PUFAs from the liver and other tissues and thus may aid in enhancing the formation of anti-inflammatory lipoxins, resolvins, protectins, maresins and prostaglandin E1 (PGE1) and suppressing the production of pro-inflammatory PGE2. As PUFAs exert anti-viral and anti-bacterial effects, the presence of adequate levels of PUFAs could inactivate HCV and HBV and prevent spontaneous bacterial peritonitis observed in cirrhosis. PUFAs, PGE1, lipoxins, resolvins, protectins, and maresins suppress TNF- α and other pro-inflammatory cytokines, exert cytoprotective effects, and modulate stem cell proliferation and differentiation to promote recovery following hepatitis, NAFLD and AFLD. Based on this evidence, it is proposed that the administration of albumin in conjunction with PUFAs and their anti-inflammatory products could be beneficial for the prevention of and recovery from NAFLD, hepatitis and cirrhosis of the liver. NAFLD is common in obesity, type 2 diabetes mellitus, and metabolic syndrome, suggesting that even these diseases could be due to alterations in the metabolism of PUFAs and other bioactive lipids.

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Hence, PUFAs and co-factors needed for their metabolism and albumin may be of benefit in the prevention and management of HBV, HCV, alcoholic hepatitis and NAFLD, and liver cirrhosis.

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Introduction

Alcoholism, hepatitis B virus (HBV), hepatitis C virus (HCV) and fatty liver disease (non-alcoholic fatty liver disease, NAFLD, and non-alcoholic steatohepatitis, NASH) are the most common causes of liver cirrhosis [1]. NAFLD and NASH are common in subjects with obesity, diabetes mellitus and coronary heart disease (CHD) [2,3]. Hence, a better understanding of the pathophysiology of HBV, HCV, NAFLD, and NASH may also provide clues for understanding obesity, diabetes mellitus, and CHD.

Both HBV and HCV can cause acute and chronic infection. Chronic HBV and HCV infections may lead to cirrhosis and hepatocellular carcinoma (HCC). In addition, patients with chronic HBV and HCV hepatitis may remain infectious and transmit the disease to other for many years. Several other causes of hepatitis include hepatitis A, hepatitis D (HDV) and hepatitis E viruses (HEV). Other infrequent causes of viral hepatitis include adenovirus, cytomegalovirus (CMV), Epstein-Barr virus (EBV) and herpes simplex virus (HSV). Both HBV and HCV may cause extrahepatic manifestations. Approximately 5% of the world's population (ie, 350 million people) are estimated to be chronically infected with HBV. Of which, about 20% will eventually develop HBV-related cirrhosis or hepatocellular carcinoma (HCC). Both HBV and HCV are transmitted via perinatal, parenteral (especially via intravenous and intranasal drug use) and sexual routes. Health workers are especially at risk of contacting both HBV and HCV infections (HBV > HCV). HBV and HCV are the most common causes of serious hepatitis (HAV is common but causes mild hepatitis, self-limiting and is transmitted through contaminated food, water and from person to person). Hence, the present discussion is restricted to HBV and HCV.

Alcohol is metabolized in the body to acetaldehyde and acetate by alcohol dehydrogenase and aldehyde dehydrogenase enzymes respectively. Acetaldehyde is hepatotoxic. HBV, HCV and alcohol cause inflammation and thus, ultimately, they lead to hepatotoxicity and apoptosis and necrosis of liver cells that can lead to fibrosis and hepatocellular carcinoma. Non-alcoholic fatty liver disease (NAFLD) is the most common cause of liver damage and is due to accumulation of excess of fat in the liver that can trigger inflammation and its consequences. Thus, inflammatory events seem to be at the centre of both infective and non-infective causes of liver damage, cirrhosis and hepatocellular carcinoma (HCC). Current knowledge suggests that there is a significant role for pro- and anti-inflammatory cytokines, bioactive lipids and oxidative stress in the pathogenesis of viral hepatitis, alcoholic hepatitis, NAFLD, liver cirrhosis, and HCC. In the current review, I surveyed critically literature pertaining to cytokines, free radicals, antioxidants, and various bioactive lipids namely polyunsaturated fatty acids (PUFAs) and their pro- and anti-inflammatory metabolites and their role in hepatitis, NAFLD and liver cirrhosis. Based on these evidences, I suggested that bioactive lipids and their metabolites and the co-factors needed for their appropriate metabolism could be exploited in the prevention and management of these diseases. Since, NAFLD is common in those with obesity, type 2 diabetes mellitus and metabolic syndrome, it is implied that similar approaches could be employed in the prevention and management of these conditions as well.

Cirrhosis is associated with PUFA deficiency

The total n-6 and n-3 PUFA levels and the levels of linoleic (LA), dihomo- γ -linolenic acid (DGLA), arachidonic acid (AA), and docosahexaenoic acid (DHA) have been reported to be significantly lower in patients with post-viral and alcoholic cirrhosis than in healthy controls, and the administration of AA, eicosapentaenoic acid (EPA) and DHA has been shown to be beneficial in HCV and diet- and chemical-induced hepatic dysfunction [4–7]. These results indicate that a deficiency of n-3 and n-6 PUFAs and the resultant decreased formation of their anti-inflammatory products, such as prostaglandin E1 (PGE1), prostacyclin (PGI2), lipoxins (LXs), resolvins, protectins and maresins, play a significant role in the pathogenesis of liver cirrhosis [8–15]. In general, PUFAs, PGE1, PGI2, LXs, resolvins, protectins and maresins seem to exert anti-fibrotic effects as they can also prevent cardiac, renal and pulmonary fibrosis [16–21] by suppressing inflammation. Lipoxin A4 (LXA4) can attenuate the expression of fibronectin, N-cadherin, thrombospondin and the notch ligand jagged 1 induced by pro-fibrotic TGF- β partly by regulating the expression of microRNA let-7c, which enhances the expression of fibronectin, N-cadherin, thrombospondin and the notch ligand jagged 1. In addition, several microRNA let-7c target genes have been found to be upregulated in fibrotic human renal biopsies, indicating that the reduced synthesis and action of LXA4 may play a significant role in fibrosis [15,21].

In this context, it is noteworthy that HBV and HCV inhibit the activity of Δ^6 and Δ^5 desaturases that are essential for the metabolism of dietary linoleic acid (LA) and alpha-linolenic acid (ALA) into their respective long-chain products gamma-linolenic acid (GLA), DGLA and AA and EPA and DHA, respectively (see Figs. 1 and 2 regarding the metabolism of essential fatty acids, EFAs, and their influence on inflammation). Thus, it is anticipated that HBV and HCV infection would cause a deficiency of GLA, DGLA, AA, EPA and DHA and their anti-inflammatory metabolites, such as LXs, resolvins, protectins and maresins, as well as PGE1 and PGI2. Such a virus-induced PUFA deficiency may further aggravate viral (e.g., HCV and HBV) infection due to the absence or decrease in the anti-viral activity of PUFAs, which are probably needed for anti-viral responses.

Pufas and their metabolites exert anti-HBV and anti-HCV effects

It is noteworthy that HBV and HCV inhibit the activity of desaturases and thus produce a PUFA (GLA, DGLA, AA, EPA and DHA) deficiency. This virus-induced PUFA deficiency seems to be a defensive mechanism developed by HBV and HCV to protect themselves from the viricidal action of these bioactive lipids. This idea is supported by the observation that several PUFAs (especially AA) and their metabolites exert anti-viral effects [22–52]. It has been reported that AA, EPA and DHA show anti-HCV activity at a physiologically relevant dose of 4 μ M (especially AA), whereas ALA, GLA and LA are effective at a much higher dose (100 μ M). In contrast, oleic acid (18:1) and saturated fatty acids, including myristic acid, palmitic acid, and stearic acid, were found to be ineffective. It is interesting to note that AA enhanced the anti-viral activity of interferon (IFN)- α [23]; additionally, IFN is known to activate

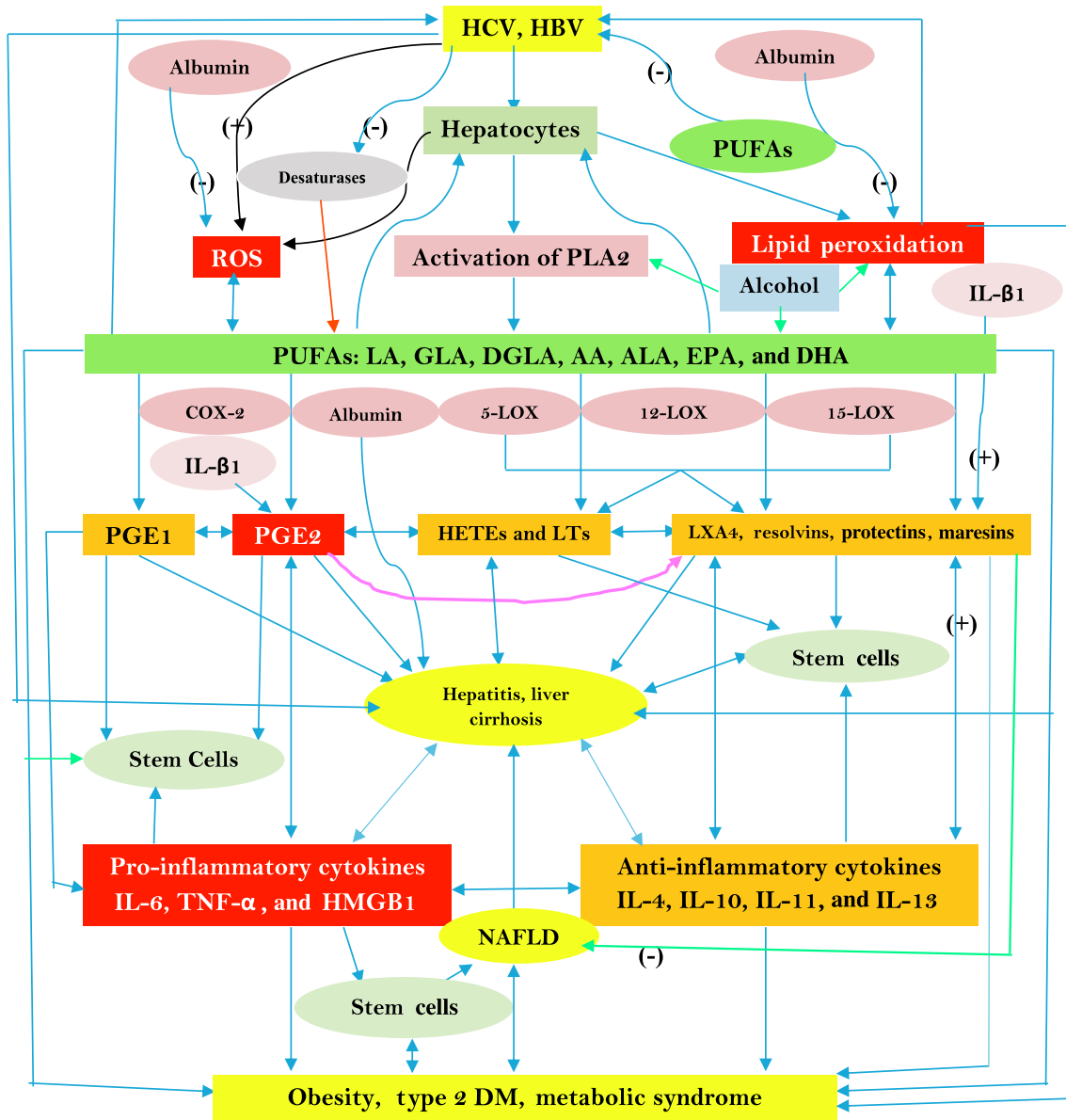


Fig. 1. Scheme showing potential role of PUFAs and their metabolites on cytokines, stem cells and liver cirrhosis. HBV, HCV, and alcohol decrease the activities of desaturases. This leads to a decrease in the formation of GLA, DGLA, AA, and EPA and DHA from their dietary precursors LA and ALA, respectively. HBV, HCV, and alcohol activate PLA2 and induce the release of various PUFAs from the liver cell membrane. These released PUFAs will be used for the formation of their respective pro- and anti-inflammatory metabolites by the action of COX-2 and LOX enzymes. HBV, HCV, and alcohol enhance the formation of pro-inflammatory products such as PGE2, LTs and pro-inflammatory cytokines such as IL-6 and TNF- α . Under normal physiological conditions, when the hepatocyte content of PUFAs are normal released PUFAs undergo peroxidation. The lipid peroxides inactivate HBV and HCV. If the hepatocytes are deficient in PUFAs, it leads to the formation of pro-inflammatory PGE2 and LTs. This causes hepatocyte inflammation (hepatitis). If PUFAs are present in adequate amounts in hepatocytes, it leads to the formation of anti-inflammatory lipoxins, resolvins, protectins and maresins that not only inhibit inflammation (hepatitis) but also inactivate HBV and HCV and protect liver from toxic actions of alcohol. PUFAs and their metabolites can also act on stem cells to enhance repair process and augment liver regeneration. IL-1 β enhances the formation of lipoxins, resolvins, protectins and maresins. Pro-inflammatory cytokines augment the production of pro-inflammatory bioactive lipids whereas anti-inflammatory cytokines enhance the formation of lipoxins, resolvins, protectins and maresins. AA and LXA4 deficiency may cause obesity, NAFLD and type 2 DM. Free radicals (ROS) generation induced by inflammatory process (including cytokines) triggered by HBV and HCV is suppressed by albumin, lipoxins, resolvins, protectins, maresins, and PUFAs especially AA. PUFAs and lipoxins, resolvins, protectins and maresins suppress the production of IL-6, TNF and HMGB1. In summary AA, EPA, DHA, LXs, resolvins, protectins and maresins inactivate viruses, suppress ROS, prevent abnormal lipid peroxidation, suppress inappropriate inflammation and thus, prevent NAFLD, hepatitis, liver cirrhosis, obesity, type 2 DM and metabolic syndrome. For further details see text.

phospholipase A2 (PLA2) and induce the release of PUFAs from the cell membrane lipid pool, indicating that one of the mechanisms by which IFN mediates its anti-viral effects is by inducing the release of PUFAs [53–56]. Thus, PUFAs released by IFN are utilized to form PGE2, a pro-inflammatory molecule and immunosuppressor, which may explain the pro-inflammatory actions of IFN. It is noteworthy that activation of the ERK, p38 and JNK signalling cascades in host cells is needed for virus-induced cyclo-oxygenase (COX)-2 activation and PGE2 formation. Paradoxically, PGE2 enhances viral replication [57]. On the other hand, AA, EPA, DHA, PGA, PG2, PGE1,

and leukotrienes (LTs) have anti-viral properties [22–52]. These results suggest that fatty acid molecules themselves and/or some of their selective products have anti-viral activity, indicating that the way PUFAs are metabolized is crucial for determining whether viruses are allowed to replicate or are inhibited from replicating, thus preventing liver damage due to HBV and HCV from occurring. It is important to note that PGA is a vasodilator, PGE2 is a vasodilator and pro-inflammatory molecule, and LTs are vasoconstrictors and pro-inflammatory in nature, whereas PGE1, LXs, resolvins, protectins and maresins are anti-inflammatory and anti-viral. Thus,

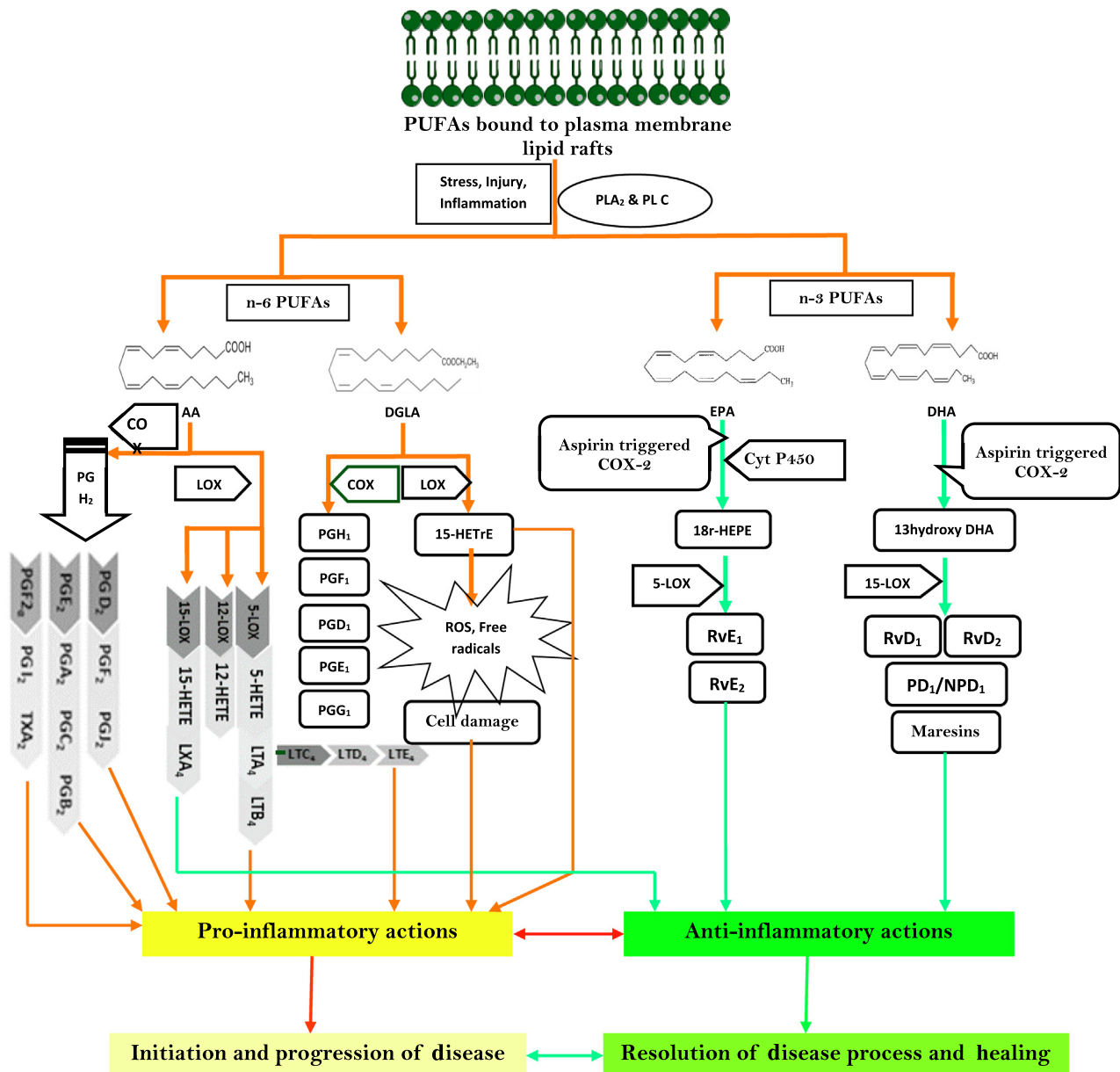


Fig. 2. Metabolism of PUFAs and formation of their pro- and anti-inflammatory products.

the final outcome of viral infections (especially HBV and HCV infections) of either the progression of hepatic damage and liver cirrhosis or the inhibition of viral replication and the resolution of hepatic damage and the inflammatory process (induced by viruses) depends on the presence of adequate amounts of PUFAs in the hepatocyte cell membranes and their release and conversion into antiviral (e.g., PGA, PGJ₂, LTs, LXs, resolvins, protectins and maresins) or viral replication-enhancing products (e.g., PGE₂). How exactly this balance between useful and harmful PUFA products is determined remains unclear.

Interactions among PUFAs, PGE₂, LXA₄ and their relationship with HBV and HCV hepatitis

It has been well documented that the anti-inflammatory metabolites of PUFAs (PGE₁, PGA, LXs, resolvins, protectins and maresins) are essential for wound healing and possess cytoprotective properties [58–62]. PUFAs, PGE₁, LXs, resolvins, protectins and

maresins inhibit IL-6 and TNF- α , which are increased in patients with hepatitis and exert cytotoxic effects [63–65]. These results, coupled with the observation that those with post-viral and alcoholic cirrhosis, HCV, and diet- and chemical-induced hepatic dysfunction have a deficiency of n-3 and n-6 PUFAs and their anti-inflammatory metabolites, PGE₁, PGI₂, LXs, resolvins, protectins and maresins [4–15], suggest that these bioactive lipids play a significant role in the pathogenesis of liver cirrhosis. These results also indicate that there could be an imbalance between pro- and anti-inflammatory bioactive lipids in cirrhosis. It is rather paradoxical that a decrease in the plasma level of AA, the precursor of LXA₄, and an increase in the concentration of pro-inflammatory PGE₂, which is also derived from AA, are observed in these patients. This findings indicate that a deficiency of AA enhances the production of pro-inflammatory PGE₂ synthesis and decreases that of LXA₄, its anti-inflammatory metabolite [12]. It is noteworthy that supplementing AA to normal healthy subjects and those with inflammation does not increase the PGE₂ level but does increase the LXA₄ level [66,67], suggesting that AA (and EPA and DHA) behave as

anti-inflammatory molecules when their concentrations are normal. On the other hand, low concentrations of these molecules (wherein the cell membrane concentrations are low) lead to the formation of pro-inflammatory molecules, such as PGE2 and PGE3 (PGE3 is also pro-inflammatory but much less potent than PGE2). AA, EPA, DHA, LXA4, resolvins protectins, maresins and PGE2 are inhibitors of IL-6 and TNF- α . Despite the inhibitory action of PGE2 on IL-6 and TNF- α , inflammation persists and progresses, suggesting that perhaps a concomitant deficiency of LXA4, resolvins, protectins and maresins is needed for the pro-inflammatory state to occur and continue. Hence, under such pro-inflammatory conditions, supplementation with AA/EPA/DHA is the best strategy for suppressing inflammation and restoring homeostasis.

It may be noted here that TNF- α and IL-6 have the ability to induce a state of EFA deficiency in cells and tissues [68]. As a result, the cellular content of various PUFAs is reduced, which can result in the decreased formation of LXA4. This EFA-deficient state triggered by excess TNF- α /IL-6 production during the inflammatory process can further enhance TNF- α /IL-6 production, which is expected to result in the aggravation and persistence of inflammation due to the lack of negative feedback control exerted by PUFAs and LXA4 on TNF- α /IL-6 production. However, paradoxically, TNF- α needs PUFAs to exert its tumouricidal effects [69,70], and under some very specific conditions, cytoprotective properties [71,72]. AA regulates TNF receptor expression, neutrophil function and free radical generation induced by TNF without being metabolized by COX and lipoxygenase enzymes [73]. Thus, AA itself seems to be capable of these actions via its incorporation into the cell membrane and the consequent alteration in membrane fluidity, which is known to alter the expression of many receptors. Another possibility is that AA is metabolized into LXA4, which exerts cytoprotective effects, modulates neutrophil function, and regulates free radical generation, properties that are similar to those of TNF- α . Although this appears paradoxical (TNF- α induces an EFA-deficient state and thus reduces LXA4 formation, whereas LXA4

inhibits TNF- α production to restore homeostasis, and PUFAs are needed for TNF- α actions), perhaps both positive and negative feedback among PUFAs, TNF- α /IL-6 and LXA4 are needed to regulate the actions of all these molecules (see Fig. 3): LXA4 is needed to control excess pro-inflammatory activity of TNF- α , whereas TNF- α is needed to induce an apparent PUFA deficiency, which is necessary to upregulate TNF- α synthesis and activity in inducing an optimal inflammatory state to trigger the resolution process, which calls for the formation of LXA4 and the synthesis of AA/EPA/DHA from dietary LA and ALA. One of the purposes of the PUFA-deficient state induced by TNF- α could be to induce the excess production of PGE2 (which inhibits TNF- α and IL-6 synthesis) that is needed for inflammation to reach its peak, in turn, triggering the resolution process. It is considered that once inflammation reaches its peak, surrounding normal cells release PUFAs from their cell membrane (possibly due to PLA2 activation by TNF- α /IL-6) that are utilized for the synthesis of LXA4/resolvins/p protectins/maresins to initiate the resolution of inflammation. In addition, it has been shown that under some very specific conditions, PGE2 can also exert anti-inflammatory effects [74] by enhancing LXA4 formation [75], which is understandable since both PGE2 and LXA4 are derived from AA, suggesting that the pro-inflammatory PGE2 pathway is redirected towards anti-inflammatory LXA4 synthesis; however, the mechanism of this redirection from PGE2 to LXA4 synthesis is not clear.

Mechanism of anti-viral action of PUFAs and their metabolites

The fact that PUFAs and some of their metabolites exert anti-viral effects [22–52] is not only interesting but also indicates that they may serve as endogenous anti-microbial compounds [24,25,28]. In such an event, decreased PUFA production or utilization could lead to the occurrence and progression of infections. The interactions of PUFAs and their metabolites with pro- and

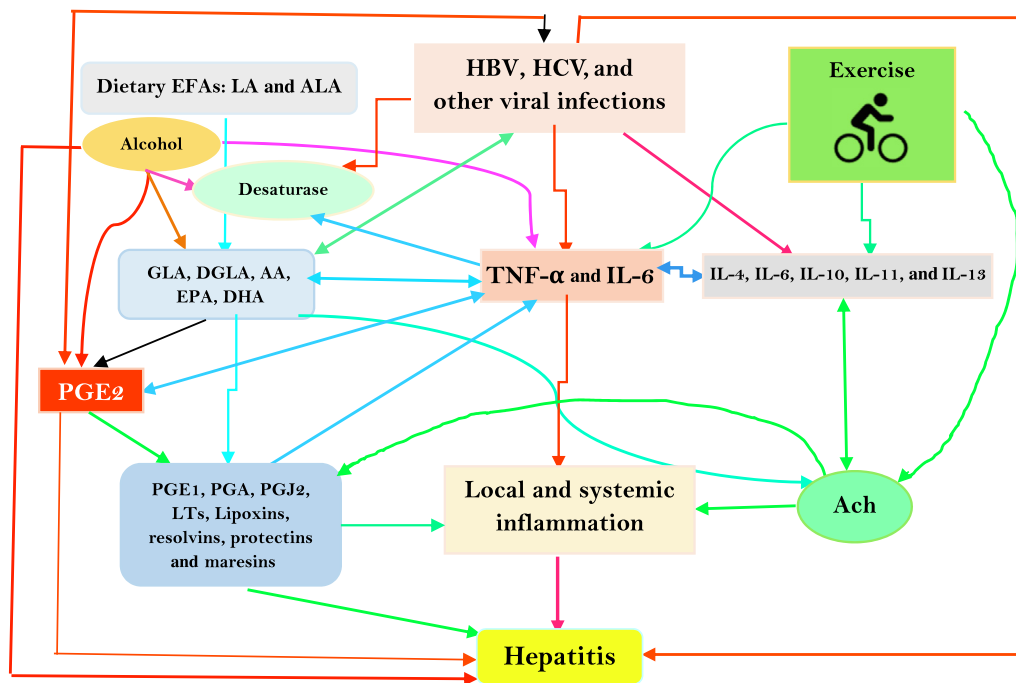


Fig. 3. Scheme showing possible role of HBV and HCV on cytokines, PUFA metabolism and development of hepatitis. HBV, HCV, and alcohol inhibit desaturases and thus, produce a deficiency of AA, EPA, and DHA. This leads to decreased formation of lipoxins, resolvins, protectins and maresins. HBV, HCV, and alcohol trigger inflammatory process by enhancing the formation of IL-6 and TNF- α , decreasing the formation of lipoxins, resolvins, protectins and maresins and enhancing the production of PGE2. Exercise enhances parasympathetic activity and acetylcholine (ACh) levels. Ach is a potent anti-inflammatory molecule and enhances the formation of lipoxins and anti-inflammatory cytokines.

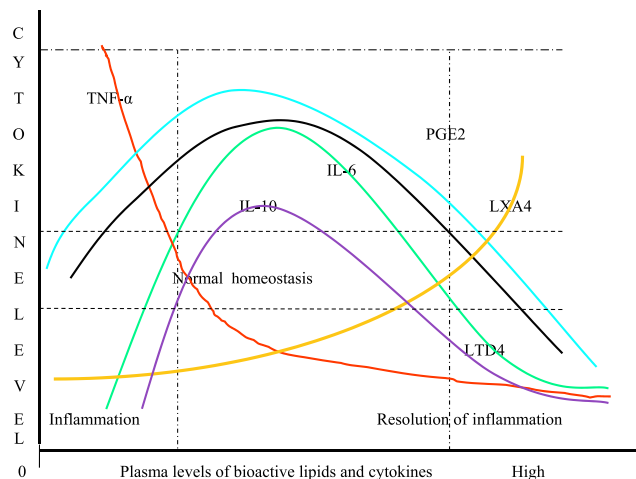


Fig. 5. A schematic representation of possible relationship among plasma levels of cytokines and PGE1, PGE2, LTs, and LXA4 in inflammation and resolution of inflammation and wound healing. Under normal physiological conditions, a delicate balance is maintained between pro- and anti-inflammatory molecules (such as IL-6 + TNF- α + PGE2 + LTD4 vs IL-10 + LXA4). When this balance is tilted more towards pro-inflammatory molecules, inflammations is initiated and perpetuated. Whenever, the synthesis and action of anti-inflammatory IL-10 and LXA4 are reduced, it leads to an increase in the production and action of IL-6, TNF- α , PGE2, and LTD4 and vice versa. But, under some very specific conditions, PGE2 may function as an anti-inflammatory molecule (see text for details). Inflammation triggered by IL-6, TNF- α and PGE2 and LTD4 is resolved by adequate formation of LXA4 and IL-10. It is not clear how exactly tissues determine as to when resolution of inflammation should start. It appears when inflammation attains its peak, it leads to suppression of PGE2/LTD4 synthesis and initiation of the formation and release of LXA4 and resolvins, protectins and maresins. It is possible, but needs firm proof, that AA, which is the precursor of PGE2 and LTD4, is redirected to form LXA4 and so suppression of inflammation. It is likely that IL-10 enhances the formation of LXA4 whereas IL-6 and TNF- α trigger the formation of PGE2 and LTD4. Similarly, LXA4 may trigger the formation of IL-10, whereas IL-6 and TNF- α enhance the synthesis of PGE2/LTD4. For details see text.

macrophages and decreasing that of M1 macrophages) to facilitate the anti-inflammatory process and augment wound healing by eliminating infection, enhancing the phagocytosis of debris at the site of inflammation and suppressing the production of pro-inflammatory PGs, LTs and TXs [28] via the inhibition of COX-2. Thus, bioactive lipids seem to have both immunologic and non-immunologic activities to account for their anti-microbial effects, which have been specifically described against Staphylococci, Streptococci, Mycobacteria, Helicobacter, and viruses, such as HBV, HCV, herpes, influenza, Sendai, Sindbis, polio, HIV, vesicular stomatitis, encephalomyocarditis, and measles [22–52].

Neutral sphingomyelinase (SMase), a hydrolase enzyme, plays an important role in sphingolipid metabolism reactions. SMase can break sphingomyelin (SM) into phosphocholine and ceramide. AA, and possibly other PUFAs, stimulate SMase activity in leukocytes and other cells and thus enhance intracellular ceramide formation, which has a tumouricidal effect [28,87,88]. Altered SMase activity drives immune evasion and facilitates tumour growth, suggesting that PUFAs, by enhancing SMase activity, can produce a significant enhancement in Th1-mediated and cytotoxic T cell-mediated anti-tumour and anti-microbial immunity. This may result in the appropriate synthesis and activity of TNF- α and other cytokines and COX-2 expression [89–92] which, in turn, facilitate the anti-microbial action of PUFAs and their metabolites.

In view of the complex relationships among HBV/HCV, cytokines, PUFAs and their metabolites and inflammation, a detailed discussion of the role of PGE1 (anti-inflammatory eicosanoid) and PGE2 (pro-/anti-inflammatory eicosanoid) in the pathobiology of liver cirrhosis is provided below.

PGE1 and its precursors in liver cirrhosis

Previously, the authors hypothesized that an imbalance in the prostaglandin system (i.e., reduced formation of PGE1 and thromboxane A2 and increased formation of PGE2) may play a role in the pathogenesis of liver cirrhosis [93]) and demonstrated that the oral administration of GLA, the precursor of DGLA, is of significant benefit to these patients [94]. This proposal was based on the observation that PGs regulate fibroblast proliferation [95] and glycosaminoglycan and collagen synthesis [95,96] and participate in the immune response and inflammation [97,98]. Corradini et al. [99] showed that cirrhotic patients have higher levels of monounsaturated fatty acids and lower levels of n-6 and n-3 PUFAs, especially DGLA, the precursor of PGE1, which were independently associated not only with the presence of cirrhosis but also with its prognosis, post-transfusion graft hepatocellular necrosis and sinusoidal congestion. These results suggest that the administration of DGLA could be beneficial to patients with liver cirrhosis, which supports our previous observation that GLA, which can be rapidly elongated to form DGLA, is beneficial in the treatment of liver cirrhosis [94]. It has been shown that 12 of 17 patients studied responded favourably to the intravenous infusion of PGE1 at 0.2 $\mu\text{g}/\text{kg}$ per hour, increased by 0.1 $\mu\text{g}/\text{kg}$ per hour every 30 min to a maximum of 0.6 $\mu\text{g}/\text{kg}$ per hour with adjustment of the dose to the patients' clinical response and maintained for up to 28 days. In this study, after 4 weeks of intravenous PGE1 therapy, the patients were transitioned to oral PGE2. No relapses were observed in these patients with hepatitis A virus (HAV) and HBV infection. Liver biopsies in all 12 surviving patients reverted to normal [100]. The remaining five non-responders showed an improvement in hepatic function, but all deteriorated and died of cerebral oedema (n = 3) or underwent liver transplantation (n = 2). These results support the original hypothesis (93) and usefulness of GLA in liver cirrhosis [94]. Several other studies [101–103] have shown a significant benefit of PGE in cirrhosis. These results lend support to the contention that a deficiency of anti-inflammatory bioactive lipids may underlie the pathogenesis of liver cirrhosis, whereas methods designed to enhance the formation of PGE1, an anti-inflammatory molecule [104–106], and other anti-inflammatory products of PUFAs, especially of GLA, which also has anti-inflammatory activity [107,108], could be of significant benefit to patients in this condition.

PGE2 in liver cirrhosis

One of the earliest investigations pertaining to the involvement of eicosanoids in the pathobiology of liver cirrhosis was performed with the idea that vasodilatory PGs could play a role in maintaining renal perfusion in patients with cirrhosis and ascites [109]. PGE2 was decreased in 14 patients with hepatorenal syndrome compared with healthy controls (2.2 ± 0.3 vs 6.3 ± 0.8 ng/h, $P < 0.01$), patients with acute renal failure (9.6 ± 2.1 ng/h) and patients with alcoholic hepatitis (9.2 ± 3.3 ng/h). In contrast, the TXB2 concentration was normal in patients with alcoholic hepatitis (0.12 ± 0.02 vs 0.15 ± 0.03 ng/mL) and minimally increased in those with acute renal failure (0.18 ± 0.15 ng/mL) but markedly elevated in those with hepatorenal syndrome (0.69 ± 0.15 ng/mL, $P < 0.001$). These data suggest an imbalance in the levels of vasodilator and vasoconstrictor metabolites of AA in patients with hepatorenal syndrome. Further, it was evident PGE2 was elevated that in those with alcoholic hepatitis compared to the normal controls (9.2 ± 3.3 ng/h vs 6.3 ± 0.8 ng/h), while there was no significant difference in the TXB2 level between the patients and controls (0.12 ± 0.02 vs 0.15 ± 0.03 ng/mL). These results are supported by the observations of Rimola et al. [110], who showed that patients with

cirrhosis without functional renal failure had a significantly higher urinary excretion of 6-keo-PGF 1α (a stable metabolite of PGI 2), TXB 2 and PGE 2 (15.9 ± 1.7 ng/h, 3.0 ± 0.3 ng/h, and 6.2 ± 1.0 ng/h, respectively) than did normal subjects (9.2 ± 0.9 , 1.3 ± 0.1 , and 2.3 ± 0.4 ng/h, respectively). The plasma renin activity, norepinephrine and anti-diuretic hormone levels were significantly increased in these patients with cirrhosis (8.0 ± 1.4 ng/mL/h, 667 ± 67 pg/mL, and 3.9 ± 0.3 pg/mL) compared to the normal controls (1.3 ± 0.2 , 275 ± 46 , and 2.4 ± 0.2 pg/mL, respectively). These results suggest that renal haemodynamics in cirrhosis depend upon a critical equilibrium between the activity of endogenous vasoconstrictors and the renal production of the vasodilators PGI 2 and PGE 2 , as well as the renin activity and norepinephrine levels. It is noteworthy that renin enhances the formation of angiotensin-II, a pro-inflammatory molecule [111–113], and that norepinephrine has pro-inflammatory activity [114–116].

Furthermore, cirrhotic patients have an altered sympatho-vagal balance with a reduced sympathetic predominance in response to passive tilting [117]. In another study, patients with cirrhosis who were awaiting liver transplantation showed significantly lower baroreflex sensitivity than did the controls (4.2 ± 0.9 vs 21.1 ± 3.8 ms/mm Hg; $P < 0.05$), and baroreflex sensitivity was lower in patients with cirrhosis with hepatic encephalopathy than in those without hepatic encephalopathy (2.6 ± 0.9 vs 6.1 ± 1.0 ms/mm Hg; $P < 0.05$). These results suggest that vagal tone is markedly depressed in cirrhosis [118]. Acetylcholine, the principal neurotransmitter of the vagus nerve, is known to have anti-inflammatory activity [119–121].

It may be noted that patients with liver cirrhosis exhibit a hyperdynamic circulatory state, as indicated by tachycardia, and an increase in cardiac output accompanied by an elevated sympathetic tone [122]. Thus, patients with cirrhosis may have increased sympathetic activity and reduced vagal tone, which may account for the increased inflammatory status that is exacerbated by enhanced plasma levels of pro-inflammatory PGE 2 .

PGE1 and inflammation

From the preceding discussion, it is evident that both PGE1 and PGE2 modulate inflammation and that to a large extent, PGE1 is anti-inflammatory, while PGE2 is pro-inflammatory. However, this is not always true.

Using a modified Draize scoring procedure, Hall and Jaitly [123] reported that topical application of 100 μ g of PGE1 can cause conjunctival redness (erythema due to vasodilatation), swelling (oedema due to increased capillary permeability), discharge, lid closure (decrease in palpebral aperture) and miosis. PGE1 and PGE2 produced almost identical dose-related increases in the scores of most of the inflammation parameters, although the oedema-related responses were consistently lower after the application of PGE2. These results suggest that under certain circumstances, both PGE1 and PGE2 have similar, if not identical, pro-inflammatory activity. It is interesting that PGE1 has been found to potentiate the oedema and pain thresholds of LTD4 and LTB4 in the rat paw. LTD4 alone had no significant effect on the development of yeast-induced paw oedema, while LTB4 significantly reduced yeast-induced oedema, and this reduction was reversed by the administration of PGE1. A significant decrease in the pain threshold was caused by PGE1, which is enhanced in the presence of LTD4. These results suggest that PGE1 plays a significant role in producing oedema but has much less of an effect on the pain threshold. Nevertheless, PGE1 has pro-inflammatory activity that seems to be modified by the presence of LTs [124].

In a study of patients with scleroderma [125], the mean baseline serum C-reactive protein (CRP) level was significantly greater

than in the patients than in the normal controls (12 ± 9.0 μ g/mL vs 1.4 ± 1.7 μ g/mL; $P < 0.001$). The mean CRP concentrations before the administration of intravenous PGE1 infusion in the PGE1-treated and placebo-treated groups were 14 ± 9 and 10 ± 9 μ g/mL, respectively. Surprisingly, after a three-day infusion of PGE1, the CRP values were 109 ± 75 and 11 ± 10 μ g/mL ($P < 0.01$) in the PGE1-treated and placebo-treated groups, respectively. The scleroderma patients showed two types of responses to the PGE1 treatment: some showed large increases (mean = 167 ± 32 μ g/mL), while others showed relatively smaller increases (mean = 22 ± 17 μ g/mL; $P < 0.005$). Those who showed greater increases in PGE1 had a shorter duration disease and greater cutaneous involvement. These results suggest that a high increase in PGE1 can induce anti-inflammatory effects and thus reduce the duration of the disease. These and other studies have revealed that PGE1 infusion can significantly benefit patients with scleroderma, a chronic inflammatory condition, as well as help relieve Raynaud's phenomenon, improve endothelial function, restore immune dysfunction, enhance the healing of digital ulcers and ultimately improve quality of life [126–131]. Thus, at high doses, PGE1 has significant anti-inflammatory activity, while at low doses, it seems to have pro-inflammatory activity or be ineffective in suppressing inflammatory events.

PGE2 and inflammation

At times, PGE2 may have anti-inflammatory activity [132–134]. The administration of human recombinant IL-1 β (0.3 μ g/kg) to rabbits with formalin-immune complex colitis 24 h before the induction of colitis increased the PGE2 level (231 ± 36 to $1,299 \pm 572$ pg/ml, $P < 0.01$) and reduced the subsequent inflammatory cell infiltration index and oedema by a significant degree compared with those in the vehicle-matched animals. The administration of ibuprofen (10 mg/kg i.v.) together with IL-1 β prevented PGE2 production, and colonic PGE2 production was found to be inversely correlated with severity of inflammation and oedema. These results suggest that pretreatment with IL-1 β 24 h before the induction of colitis reduces inflammation by a mechanism that requires PG synthesis and that PGE2 may exert anti-inflammatory effects [135]. Furthermore, PGE2 (50 nm) attenuated the lipopolysaccharide (LPS)-induced mRNA and protein expression of chemokines, including monocyte chemoattractant protein 1, IL-8, macrophage inflammatory protein 1 α and 1 β , and interferon-inducible protein 10. In addition, PGE2 inhibited the TNF- α -, IFN- γ -, and IL-1 β -mediated expression of chemokines. A selective EP4 (PGE2 receptor) antagonist reversed PGE2-mediated suppression of chemokine production, suggesting that endogenous PGE2 plays a role in the modulation of inflammation by suppressing macrophage-derived chemokine production via the EP4 receptor [134]. Thus, PGE2 has an anti-inflammatory effect on macrophages by suppressing the stimulus-induced expression of pro-inflammatory genes, including those encoding chemokines.

Subsequent studies demonstrated that PGE2 pretreatment inhibited LPS-induced nuclear factor kappa B1 (NF-kB1) p105 phosphorylation and degradation in mouse bone marrow-derived macrophages and RAW 264.7 cells through EP4-dependent mechanisms. The enhanced expression of PGE receptor type 4-associated protein (EPRAP) inhibited NF-kB activation induced by pro-inflammatory stimuli in a dose-dependent manner. In co-transfected cells, EPRAP directly interacted with NF-kB1 p105/p50 and formed a complex with EP4, while in EP4-overexpressing cells, PGE2 enhanced the protective action of EPRAP against stimulus-induced p105 phosphorylation. On the other hand, EPRAP silencing in RAW 264.7 cells impaired the inhibitory effect of PGE2-EP4 signalling on LPS-induced p105 phosphorylation, whereas EPRAP

knockdown and NF- κ B1 deficiency in macrophages attenuated the inhibitory effect of PGE2 on LPS-induced MIP-1 β production. Thus, PGE2-EP4 signalling augments NF- κ B1 p105 protein stability through EPRAP after pro-inflammatory stimulation, limiting macrophage activation [135]. These results emphasize the fact that under certain specific conditions, PGE2 behaves as an anti-inflammatory molecule [136–138]. In fact, it has been shown that blocking the 15-PGDH enzyme that leads to an increase in the half-life of PGE2 enhances tissue regeneration and repair in the bone marrow, colon, and liver [138]. These results indicate that the increased plasma level of PGE2 observed in those with liver cirrhosis could be an attempt on the part of the body to augment hepatic regeneration. In addition, the pro- and anti-inflammatory actions of PGE2 may depend on the presence of other AA metabolites, such as LTB4 and LTD4, as discussed above [124], and the ability of PGE2 to trigger the anti-inflammatory cascade. Thus, the pro- and anti-inflammatory actions of PGE1 and PGE2 are only relative and depend on the dose of PGs, the duration of tissue exposure to PGs, and the presence or absence of other PGs, LTs and TXs. It is also noteworthy that the LXA4 level is decreased in cirrhosis and that LXA4 protects hepatocytes from carbon tetrachloride-induced toxicity [12,14].

Optimal inflammation is critical for the initiation of anti-inflammatory events

It is known that excess of PGE2 and LTs production could trigger the production of anti-inflammatory LXA4 from AA. Enhanced production of PGE2 and LTs seen on exposure to whole-body gamma radiation, cobalt 60, and cyclotron neutrons could stimulate LXA4 production at the expense of the pro-inflammatory AA-derived LTB4. It was reported that the production of the anti-inflammatory metabolite 15-HETE (LXA precursor) peaked at 72 h following radiation/UVB exposure coincided with the gradual decrease in PGE2 and LT formation. Thus, there seems to be a gradual and smooth shift in the synthesis of eicosanoids from pro-inflammatory PGE2 and LTs to 15-HETE and LXs that could herald the initiation of resolution of the radiation-induced damage [139–141]. This implies that the initial enhanced synthesis of pro-inflammatory PGE2 and LTs is essential to trigger and initiate the formation of anti-inflammatory LXA4. Furthermore, PGE2 can enhance the production of IL-10, an anti-inflammatory cytokine [142]. IL-6 release is enhanced by PGE2 in the presence of IL-10, whereas both IL-10 and PGE2 inhibited the LPS-stimulated production of IL-6 and TNF- α , and the selective inhibition of COX-2 or the addition of anti-IL-10 reversed these effects [143]. Additionally, exogenous IL-10 expression suppressed COX-2 production [144]. These results suggest that PGE2 induces the production of IL-10, which, in turn, downregulates IL-6, TNF- α , and COX-2 activity to restore homeostasis [142–144]. PGE2, a pro-inflammatory molecule, may, in fact, trigger anti-inflammatory actions by augmenting the synthesis of LXA4 and IL-10, which may explain the paradoxical pro- and anti-inflammatory actions reported by several investigators. These results suggest that the degree, progression and resolution of inflammation depend on the local concentrations of PGE1, PGE2, LTs, LXA4, TNF- α , IL-10 and IL-6 and the orderly fashion in which the transition from pro- to anti-inflammatory events/molecules occurs, allowing wound healing and homeostasis restoration to take place (see Figs. 4 and 5).

An interesting report by O'Brien et al. [145] demonstrated that the concentration of the pro-inflammatory and immunosuppressive eicosanoid PGE2 was elevated in patients with acute decompensation of cirrhosis and could be restored to normal by albumin and indomethacin, a non-selective COX inhibitor, but not by a 12-lipoxygenase inhibitor. These results led to the

suggestion that the intravenous administration of human serum albumin to patients with acutely decompensated cirrhosis could not only lead to an increase in the serum albumin level but also enhance the amount of PGE2 bound to albumin, leading to a decrease in free PGE2 to restore immune competence [146]. This finding suggests that an altered PUFA metabolism and an imbalance in the eicosanoid system play significant roles in the pathogenesis of liver cirrhosis as previously proposed [93,94].

Albumin, PUFA mobilization, and TNF- α in liver cirrhosis

In this context, it is interesting that albumin mobilizes PUFAs from the liver and aids in the formation of LXs, resolvins, and protectins that inhibit oxidative stress-induced apoptosis and COX-2 expression [147–150]. In liver cirrhosis and other critical illnesses associated with hypoalbuminemia, the ability of albumin to mobilize PUFAs is limited; thus, the formation of LXs, resolvins, and protectins will be inadequate, which may be responsible for the increased morbidity and mortality associated with these conditions. Furthermore, following albumin treatment the plasma concentrations of TNF- α , IL-6, and macrophage inflammatory protein 2 were significantly lower and that of IL-10 was significantly higher in an animal model of haemorrhagic shock [149–151], suggesting that hypoalbuminemia decreased the formation of LXs, resolvins, and protectins, tilting the balance more towards pro-inflammatory events. The ability of albumin to mobilize PUFAs from the liver is dependant on the hepatic stores of PUFAs, which could be one variable that influences the level of LX, resolvins, and protectin production. In addition, TNF- α caused a marked decrease in the PUFA total phospholipid (PL) content and induced an EFA-deficient state reminiscent of long-term malnutrition [152], as confirmed by the observation that TNF administration to healthy well-nourished rabbits produced hypoalbuminemia [153]. Hence, enhanced circulating levels of TNF- α and other pro-inflammatory cytokines seen in liver cirrhosis, sepsis and other critical illnesses cause not only hypoalbuminemia but also PUFA deficiency that results in reduced formation of lipoxins, resolvins and protectins.

The activity of the enzymes (COX and 5-, 12-, and 15-lipoxygenases) that are needed for the formation of LXs, resolvins, and protectins may also vary depending on the underlying clinical condition, which could contribute to the reported variations in the response to albumin therapy. Albumin kinetics are altered in liver cirrhosis and other critical illnesses such that the half-life is shorter and the transportation rate is higher in the critically ill compared to the controls [149], which could be yet another variable influencing the formation of LXs, resolvins and protectins.

Furthermore, it has been shown that (i) HCV induced ROS formation and activated NF- κ B, which mediated the activation of COX-2 and thus enhanced the levels of PGE2 in HCV-expressing cells, providing a mechanism by which HCV-induced inflammation is relevant to the development of liver cirrhosis associated with viral infection [154]; (ii) LXs, resolvins and protectins have antagonistic activity against PGE2, suppress PGE2 synthesis and exert anti-fibrotic effects [7–15]; and (iii) resolvins and possibly LXs and protectins have anti-bacterial activity [22], which may explain why bacterial infections are common in cirrhosis, whereas PUFAs themselves seem to have anti-bacterial, anti-viral and anti-fungal activities [28]. In particular, AA, EPA and DHA have anti-HCV activities; AA is effective at 4 μ M, which falls within the range of physiologically relevant concentration [26,27]. HCV-infected hepatocytes produce ROS, which initiate lipid peroxidation. When incubated with AA without lipid-soluble antioxidants, Huh7 cells harbouring an HCV replicon (Huh7-K2040 cells) exhibited a sharp reduction (>95%) in HCV RNA and a simultaneous increase in lipid peroxides that could be prevented by vitamin E.

Thus, in the presence of AA and in the absence of lipid-soluble antioxidants, such as vitamin E, HCV replication induced lipid peroxidation that reduced the level of HCV RNA. Thus, AA and possibly other PUFAs (such as EPA and DHA) inhibit HCV (and possibly HBV) replication via a lipid peroxidation-dependent process [26,28].

Conclusions and therapeutic implications

Based on the preceding discussion, it is suggested that (i) HCV and HBV-enhanced TNF- α production induces a deficiency of PUFAs (especially AA, EPA and DHA); (ii) HCV- and HBV-induced ROS production and lipid peroxidation further aggravates the PUFA deficiency, which, in turn, may enhance viral proliferation; (iii) virus-triggered COX-2 activity leads to an increase in PGE2 production; (iv) decreased hepatocyte AA, EPA and DHA levels lead to decreased LX, resolvins and protectin production; (v) the enhanced TNF- α production due to viral (HCV and HBV) infection causes hypoalbuminemia that further aggravates the deficiency of LXs, resolvins and protectins; and (vi) an imbalance between pro-inflammatory PGE2 and anti-inflammatory LXs, resolvins and protectins (and decreased PGE1 formation due to the PUFA deficiency, especially that of DGLA) may manifest in the form of immunosuppression, inflammation and inappropriate bacterial infections in liver cirrhosis. Albumin is beneficial in patients with cirrhosis (provided there are sufficient hepatic stores of PUFAs) due to its ability to mobilize PUFAs and enhance the formation of LXs, resolvins and protectins. Thus, albumin complexed with PUFAs, LXs, resolvins and protectins could be beneficial in treating liver cirrhosis. Additionally, the plasma levels of various PUFAs, PGE2, PGE1, PGI2, LXs, resolvins and protectins may be useful as prognostic markers of liver cirrhosis.

These observations indicate that the plasma levels of LXs, resolvins, and protectins may reflect the efficacy of albumin therapy; albumin could be co-administered with EPA/DHA/PUFAs to enhance the formation of LXs, resolvins, and protectins (apart from reducing or quenching PGE2) and thus improve the prognosis of cirrhosis. Thus, the plasma levels of PUFAs, PGE2, LXs, resolvins, and protectins could be used to predict the beneficial effects of albumin and the prognosis of cirrhosis.

Both alcohol-induced hepatitis and NAFLD are known to result in liver cirrhosis. Alcohol (ethanol) is known to inhibit the activities of desaturases that are essential for the formation of AA, EPA and DHA from dietary LA and ALA and thus could result in a PUFA deficiency and the reduced formation of PGE1, LXs, resolvins, protectins and maresins, which may explain why chronic and excess alcohol consumption leads to liver cirrhosis [3,155–157]. Similarly, even NAFLD is characterized by a PUFA deficiency and the reduced formation of LXs, resolvins, protectins and maresins, suggesting that supplementation with various PUFAs, PGE1, LXs, resolvins, protectins and maresins may resolve hepatic damage/dysfunction [4,6,7,158–160]. Although the role of the gut microbiota in the pathogenesis of liver cirrhosis is not discussed here, there is substantial evidence to suggest that PUFAs have a favourable influence on the gut microbiome, which may explain yet another mechanism by which bioactive lipids are beneficial in liver dysfunction/liver diseases [80,161].

Our recent studies showed that obesity, type 2 diabetes mellitus and metabolic syndrome induced by streptozotocin and high fat diet can be prevented by supplementation of AA and its anti-inflammatory metabolite LXA4 [58–62]. It was noted that streptozotocin and high fat diet inhibit the activities of desaturases and decrease the formation of AA and LXA4. Patients with type 2 DM showed reduced plasma concentrations of AA and LXA4 [162,163]. These results indicate that obesity, type 2 DM and metabolic syndrome, conditions in which NAFLD is common, are also

characterized by altered PUFA metabolism. This suggests that, in all probability, bioactive lipids play a significant role in these conditions and so, are likely to be of benefit in their prevention and management [164].

Based on the preceding discussion, it is suggested that bioactive lipids play a significant role in the pathogenesis of alcoholic liver disease, NAFLD and virus-induced liver cirrhosis. Hence, it is suggested that supplementation and/or infusion of appropriate amounts of albumin, PUFAs, and co-factors that are needed for the adequate formation of PGE1, PGI2, PGA, lipoxins, resolvins, protectins and maresins such as vitamin C, pyridoxine, vitamin B12 and folic acid could be employed to prevent, manage, and reverse hepatic dysfunction/disease [4,6,7,58,59,93,94,158–160].

Conflict of interest

The authors declared that there is no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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