Biochemistry of Non Infectious Hepatitis - A Review

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ABSTRACT

Hepatitis is a medical condition defined by inflammation of the liver and characterized by the presence of inflammatory cells in the liver parenchyma. There are several types of hepatitis including viral, autoimmune, fatty liver, alcoholic, drug-induced and toxin-induced hepatitis. Many causes and mechanism of pathogenesis of some of these types of hepatitis particularly the non-infectious/non-viral hepatitis still remain to be understood despite the economic and health burden it places in the health, economic and scientific realm. However, research is a loose ended and continuous process hence proper understanding of present findings will provide a background for further studies in a bid to unravel some of the mysteries in non-infectious hepatitis hence a more efficient and effective approach of treatment/management of the ailment. This article attempts to discuss the causes of non-infectious forms of hepatitis which can be a sequel of metabolism disorder/syndrome, nutrition, toxification due to xenobiotics and or genetic disorder / predisposition. Possible mechanisms of pathogenesis that were captured include induction of oxidative stress, organelles dysfunction, apoptosis, necrosis, genetic modulation, electrolyte imbalance, uncoupling of mitochondrial electron transport chain among others.

Key Words: hepatitis; non-infectious/non-viral hepatitis; mechanism; pathogenesis; toxification; xenobiotics

INTRODUCTION

Hepatitis is a medical condition defined by inflammation of the liver and characterized by the presence of inflammatory cells in the liver parenchyma.

There are several types of hepatitis including viral, autoimmune, fatty liver, alcoholic, drug-induced and toxin-induced hepatitis [1][2][3]. In spite of the fact that hepatitis is mostly caused by viruses [4], there is a considerable rise in non-infectious/non- viral hepatitis globally probably due to increasing risk factors such as industrialization, life style and xenobiotics. The liver, located between the absorptive surfaces of the gastrointestinal tract is a vital organ central to the metabolism of virtually every endogenous and exogenous substances [5]. It plays an astonishing array of vital functions in the maintenance, performance and regulating homeostasis of the body. Thus, it is involved in almost all the biochemical pathways to growth, fight against disease, nutrient supply, energy provision and reproduction [6]. As a result, the liver cells/tissue is constantly exposed to harmful substances which expose it to toxification, inflammation and death. These toxins inflict varying degree of damage to the hepatocytes depending on the degree of toxicity and period of exposure to the substance. Alcohol has for long been proven to be a hepatoxin [7] and several factors including ethanol metabolism–associated oxidative stress, glutathione depletion, abnormal methionine metabolism, malnutrition, ethanol-mediated induction of leakage of gut endotoxins, and subsequent activation of Kupffer cells have been reported in earlier studies to play role in the pathogenesis of alcohol liver disease. In the same vein, alcohol mediates changes in epigenetic features, microRNAs (miRNAs), and stem cells, which could also

contribute to alcoholic liver disease (ALD) [8].

Drug-induced liver injury (DILI) are recognized and clinically significant cause of acute, acute-on-chronic and, less commonly, chronic liver disease. Drugs remain a significant, if not the leading, cause of acute liver failure in the developed world and a prominent aetiological factor in the developing world. The liver enzyme pattern in a patient with suspected DILI may be the signature pattern for a given drug [9]. The spectrum of drug-induced liver injury ranges from minimal, nonspecific alterations in biochemical tests of no clinical consequence to acute hepatitis, chronic hepatitis, acute liver failure, prolonged cholestatic disease, and even cirrhosis and hepatic tumors. Furthermore, some drugs have been shown to cause fatty liver (simulating alcohol-induced liver disease) and granulomas (simulating sarcoidosis) as well as others that lead to acquired phospholipidosis or predispose to development of the Budd-Chiari syndrome [10]. Excessive fat in the liver in the absence of alcohol consumption called non-alcoholic fatty liver disease (NAFLD) predisposes it to the development of non-alcoholic steato-hepatitis NASH and is a significant risk factor for developing cirrhosis and its complications, including hepatocellular carcinoma (HCC). Bio-chemicals, (obesity-related cytokines) such as interleukin-6 (IL-6), adiponectin, leptin and tumor necrosis factor alpha (TNF- α) may play important roles in the development of NAFLD. The prevalence of NASH is 3% and 20% in non-obese and obese subjects, suggesting that excessive fat is a risk factor to liver disease[11]. As many as 80% of subjects with non-alcoholic fatty liver disease have evidence of metabolic syndrome and it is important to realize that patients with non-alcoholic fatty liver disease may progress to cirrhosis[12].

Chemical messengers called cytokines play an important role during the body's initial response to infection (i.e. acute inflammation). Cytokines attract and activate components of the immune system, promote blood clotting and facilitate the release of additional chemical messengers. In addition, cytokines induce the liver to shift its physiological function, emphasizing inflammatory and immune responses at the expense of normal metabolism. The high level of cytokine results in liver disease termed as inflammatory liver disease [13]. Toxic chemicals such as the dry cleaning agent carbon tetrachloride which is also used as industrial solvents, a herbicide called paraquat, organophosphorus (an insecticide), are some of the most common chemicals that exhibit hepatotoxicity [14] through the induction of oxidative stress, cell death, apoptosis and inflammation[15]. This occurs as a result of imbalance of oxidation and antioxidant systems, leading to the generation of overloaded free radicals and reduction of antioxidant capacity. Liver diseases related with oxidative stress will develop from subclinical icteric hepatitis to hepatic fibrosis, liver cirrhosis and even hepatocellular carcinoma [16]. Understanding the mechanism and evolution of these hepatic diseases is critical in identifying effective approaches for their management and or treatment.

This review article briefly summarizes the causes and possible mechanisms of non-infectious hepatitis which can serve as a reference material, provide a baseline for further research or forms the background for developing a standard book in the field of hepatology.

MOLECULAR BASIS OF ALCOHOL-INDUCED HEPATITIS

Alcoholism or alcohol use disorder is defined as overconsumption of ethanol (men > 30 g/day and women > 20 g/day) [17]. Liver being central to the metabolism of virtually everything that enters the gut is exposed to the toxicity of different substances that passes through it including alcohol. Alcoholic liver diseases (ALDs), including acute alcoholic liver injury, liver failure, alcoholic fatty liver disease (AFLD), and alcoholic steatohepatitis (ASH) are the

implications of alcoholism overtime [18]. ALD presents a broad spectrum of disorders, ranging from simple fatty liver to more severe forms of liver injury, including alcoholic hepatitis (AH), cirrhosis, and superimposed hepatocellular carcinoma (HCC). Ethanol metabolism–associated oxidative stress, glutathione depletion, abnormal methionine metabolism, malnutrition, ethanol-mediated induction of leakage of gut endotoxins, subsequent activation of Kupffer cells, inflammation, changes in epigenetic features, microRNAs (miRNAs), and stem cells have been found to be central in the initiation and progress of ALD [8].

In 1979, Baraona and Lieber [19] explained steatosis, the earliest response of the liver to alcohol abuse, to be characterized by the accumulation of fat (mainly triglycerides, phospholipids, and cholesterol esters) in hepatocytes. Early studies indicated that alcohol consumption increases the ratio of reduced nicotinamide adenine dinucleotide/oxidized nicotinamide adenine dinucleotide in hepatocytes, which disrupts mitochondrial oxidation of fatty acids and results in steatosis. Studies have also indicated that alcohol exposure, directly or indirectly, regulates lipid metabolism-associated transcription factors which results in the stimulation of lipogenesis and inhibition of fatty acid oxidation. In the same vein, Alcohol consumption has been reported to inhibit fatty acid oxidation in hepatocytes mainly via inactivation of the peroxisome proliferator-activated receptor (PPAR); a nuclear hormone receptor that controls transcription of a range of genes involved in free fatty acid transport and oxidation which all amount to steatosis [20]. Alcoholic hepatitis, a syndrome characterized by infiltration of the liver by inflammatory cells and hepatocellular injury develops in patients with steatosis and is usually associated with progressive fibrosis and studies have shown that the pathogenesis of the disease is multifactorial [21].

In hepatocytes, ethanol is primarily metabolized into acetaldehyde by alcohol dehydrogenase in the cytosol, cytochrome P450 in microsomes, and catalase in peroxisomes. Ethanol metabolism generates reactive oxygen species and causes lipid peroxidation, mitochondrial glutathione depletion, and S-adenosylmethionine depletion; all of these subsequently prime and sensitize hepatocytes to injury. Acetaldehyde is rapidly metabolized into acetate by aldehyde dehydrogenase in mitochondria. Acetaldehyde is a reactive compound that is highly toxic to hepatocytes due to its ability to form variety of protein and DNA adducts that promote glutathione depletion, lipid peroxidation, and mitochondrial damage [22][8]. Although acetate has no direct hepatotoxicity, it is believed to regulate the inflammatory response via the up-regulation of proinflammatory cytokines (interleukin-1β (IL-1β), and IL-18) in macrophages [23][8] which leads to the production of large caspase-1-activating protein complexes called inflammmasomes. Inflammasome activation has been shown to induce cell pyroptosis, a process of programmed cell death distinct from apoptosis [24]. Alcoholism was also reported to upregulate cytokine production through increasing intestinal permeability to endotoxins and production of reactive oxygen species from the metabolism of ethanol. Excess cytokines generated via this mechanism leads to hepatic injuries and inflammations [13].

Hepatocyte apoptosis is an important pathologic feature of human ALD. Apoptosis results from multiple mechanisms such as ethanol-mediated hepatotoxicity, induction of oxidative stress, inhibition of survival genes (c-Met), and induction of proapoptotic signaling molecules (TNF- and Fas ligand)[25].

Alcoholism has been reported to causes epigenetic changes that contribute to alcohol-induced organ damage, including ALD [26]. Ethanol was found to affect the metabolism of methionine and thereby DNA

methylation. Methionine metabolism occurs primarily in the liver, where homocysteine is methylated to methionine and then S-adenosylmethionine (SAMe) in a transmethylation reaction catalyzed by methionine adenosyltransferase [27]. SAMe is a principal methyl donor in methylation reactions and has an important role in inducing DNA and histone methylation. Long-term ethanol consumption reduces hepatic levels of SAMe and consequently reduction in DNA and histone methylation, increasing expression of genes that regulate the endoplasmic reticulum stress response which by implication increases alcoholic liver injury [28]. Kendrick *et al*. [23] reported that alcoholism was also found to up-regulate histone acetylation in macrophages, contributing to the up-regulation of several proinflammatory cytokines that could promote AH.

MOLECULAR BASIS OF DRUG INDUCED HEPATITIS

Drug-induced liver injury (DILI) a term synonymous with drug-induced hepatotoxicity can simply be said to be a liver injury induced by a drug or herbal medicine resulting in liver test abnormalities or liver dysfunction with a reasonable exclusion of other potential aetiologies [9]. Su (2020) [29] also defined DILI as a liver injury caused by various drugs, herbs, or other xenobiotics leading to abnormalities in liver function and may be referred to be hepatitis, liver cirrhosis, and liver necrosis when supported by liver biopsy findingsDrug-induced liver injury DILIs are significant cause of acute, acute-on-chronic and, less commonly, chronic liver disease whose clinical presentation may range from a mildly deranged liver profile to acute liver failure, encephalopathy and jaundice. Although uncommon, cirrhosis may result from a long-standing DILI [9][29]. More than 900 drugs and herbs have been reported to cause liver injury and are acute dose- dependent [6]. According to[29] DILI is a concern in several clinical fields but often overlooked and sometimes progresses into a chronic liver injury that lasts more than six months and can reach hepatic failure, which requires liver transplantation, or death. The DILI spectrum is variable and broad which in most cases leads to hepatocytes damage, but cholangiocytes, stellate cells, and sinusoidal endothelial cells can also be damaged, and several other types of cells can also be damaged simultaneously. Drug-induced liver injury DILI can manifest itself as almost any kind of liver disease, from acute hepatitis to chronic hepatitis, fatty liver or steatohepatitis, vascular damage, liver cirrhosis, and even hepatic tumors [30].

Earlier studies reported in the work of Su, (2020) [29] mentioned that DILI is caused by intrinsic and idiosyncratic reactions, and sometimes, both may occur together. Intrinsic liver injury is dose dependent and predictable while idiosyncratic liver injury is on the other hand divided into immunoallergic and metabolic idiosyncratic reactions regardless of dose, and it is unpredictable. However, Lammert *et al* [31] reported that idiosyncratic liver injury is dose- dependent which contradicts the report of the earlier studies.

In current concepts of DILI, the hepatocyte injury mechanism is divided into 3 stages: hepatocyte injury or direct cell stress (first stage), mitochondria permeability transition (second stage) and hepatocyte death or apoptosis and necrosis (last stage) [32][29]. Hepatocytes can be injured directly by drug metabolites or parent drugs though less often through direct cell stress, mitochondrial function targeting, or trigger specific immune reactions [33]. Direct stress can be induced through mechanisms such as depletion of glutathione (GSH), or binding to enzymes, lipids, nucleic acids and other cell structures. In the case of initial targeting of mitochondria, reactive metabolites or parent drugs uncouple or inhibit the mitochondrial respiratory chain causing ATP depletion and increased concentrations of reactive oxygen species (ROS), inhibit β- oxidation leading

to steatosis, damage mitochondrial DNA or interfere with its replication, or directly cause mitochondrial permeability transition (MPT), i.e. opening of the "MPT pore" located in their inner membrane. Specific immune responses involving cytotoxic T-cells with concomitant release of inflammatory cytokines can be evoked by reactive metabolites that covalently bind to proteins and are subsequently recognized as neo-antigens (hapten formation). Their subsequent major histocompatibility complex (MHC)-dependent presentation on antigen presenting cells may then activate formation of antibodies against haptens or autoantibodies against cell structures such as CYP450 enzymes [32]. Impaired mitochondrial function and energy production leads to apoptotic or necrotic cell death. Mitochondrial permeability transition MPTallows massive influx of protons through the inner mitochondrial membrane, which stops mitochondrial ATP synthesis. Mitochondrial ATP depletion resulting from MPT or other direct mechanisms of mitochondrial damage mentioned above causes matrix expansion and mitochondrial outer membrane permeabilization and rupture with release of cytochrome c and other pro-apoptotic mitochondrial proteins from the intermembrane space into the cytosol [34].

In addition to that, drugs also induce cholestasis due to their effects on drug transporters, various hepatocellular changes, and altered bile canaliculi dynamics. Drug metabolite that exits through the canalicular membrane also damages the cholangiocytes, causing cholestasis [35]. Liver injury may also be further exacerbated due to transmission of hepatic injury and inflammatory signals to neighboring cells through other gap junctions, and the liver injury may be targeted to non-parenchymal cells other than hepatocytes and cholangiocytes[36]. Pandit *et al*. [6] reported that acetamenophen was the highest drug responsible for drug- induced acute liver injury in the United States. It is the prime example of a drug that produces a predictable dose-dependent liver injury and remains the leading cause of acute liver failure in the developed world, with approximately half of cases being unintentional overdoses due to inadequate knowledge about its toxicity potentials and suicide attempts accounting for the rest[9]. In overdose, the analgesic/antipyretic acetaminophen produces centrilobular hepatic necrosis [6]. This is characterized by nuclear pyknosis and eosinophilic cytoplasm followed by large excessive hepatic lesion. The covalent binding of N-acetyl-parabenzoquinoneimine, an oxidative product of paracetamol to sulphydryl groups of protein, result in lipid peroxidative degradation of glutathione level and thereby, produces cell necrosis in the liver [37]. Studies using rat liver mitochondria and freshly isolated rat hepatocytes showed that diphenylamine, which is common in the structure of non- steroidal anti-inflammatory drugs (NSAIDs), uncouples oxidative phosphorylation, decreases hepatic ATP content and induces hepatocyte injury [6].

MOLECULAR BASIS OF NON-ALCOHOLIC FATTY LIVER- INDUCED HEPATITIS

Nonalcoholic fatty liver disease (NAFLD) is a clinicopathological syndrome caused by genetic, environmental, and metabolic stress-related factors and clinically manifests with fat accumulation in hepatocytes; specifically fat accumulation exceeding 5% of hepatic wet weight, or changes in the fatty content taking place in over 1/3 of hepatocytes per unit area even though the overconsumption of alcohol is excluded[38]. According to [39] NAFLD is a disease related to gene, environment and metabolic stress. Its causes include metabolic factors (e.g., diabetes mellitus), nutritional factors (e.g., obesity), drug, physical and chemical factors (e.g., corticosteroid), hereditary factors, systemic diseases, biological factors (e.g., microbial infection caused by virus and bacteria), mental, psychological and social factors, sedentary lifestyle, a high fat and high-

calories diet, and lack of exercise. In addition, NAFLD incidence remarkably increased with the increase of chemical pollution [40][41]. In recent studies reported by [41], improvement of the living standards, lifestyle change, aging of the population, and rise in obesity were among the risk factors associated with alcoholic liver disease.Pathologically, it can progress from nonalcoholic fatty liver to nonalcoholic steatohepatitis (NASH), fatty hepatic fibrosis, and cirrhosis[42][1][41]. Nonalcoholic fatty liver disease is strongly associated with the metabolic syndrome (as patients often possess the corresponding features of insulin resistance (IR), dyslipidemia, type 2 diabetes mellitus (T2DM), and obesity), and oxidative stress [43][44].This disease has been recognized as an emerging health problem worldwide[45]and is among the causes of cryptogenic cirrhosis and is expected to rise as rates of obesity and the metabolic syndrome reach epidemic proportions worldwide. Although NAFLD has mild symptoms, its damage is great, its pathogenesis still remains not fully understood despite the increasing number of studies being carried out on the disease in the scientific domain[46].

Insulin Resistance is one of the causes of NAFLD as stated earlier. This term implies that the sensitivity of the body to the produced insulin is reduced due to various causes. To maintain a stable blood sugar level, the body secretes even more insulin to compensate, resulting in hyperinsulinemia [47] leading to an increase in glycolysis to produce more fatty acids. Insulin resistance leads to an increase in free fatty acids due to its impact on lipid metabolism, which is beyond hepatic metabolic ability, resulting in excessive fatty acids accumulated in the liver. In addition, the secretion of very-low-density lipoprotein decreases so that TG increases. The sequel of the IR results to damages in the biochemical machinery of the hepatocyte, which increases TG storage and impairs energy production by mitochondrial

oxidation [1]. Obesity, most especially abdominal visceral fat has been found to be associated with NAFLD. Wolf *et al.* [48] reported that abdominal visceral fat has a lipolytic nature and is in close proximity with the portal system.It is also more lipolytically active than subcutaneous fat due to its lower sensitivity to insulin and a higher concentration of beta-receptors. Furthermore, visceral fat is known to drain directly into the portal system which exposes the liver to large amounts of free fatty acids that may be oxidized or synthesized to triglycerides and stored (steatosis).

In circumstances of lipid metabolism disorders, synthesis and secretion of triglyceride transfer protein and apolipoprotein decrease due to various causes. This reduces the exo-hepatic transport of triglycerides; thus, they accumulate in the liver resulting in NAFLD [49].

Mitochondrial dysfunction which is usually aggravated by mitochondrial DNA damage, disorders of energy metabolism, oxidative stress and lipid peroxidation, mitochondria-mediated hepatocellular apoptosis, disorders of fatty acid metabolism and abnormal mitophagy have been reported to play critical role in the mechanism of NAFLD[41]. This can be attributed to the central role played by mitochondria in complex processes, including the generation of energy and reactive oxygen species (ROS), maintaining calcium homeostasis, and adjusting apoptosis and lipid metabolism[50]. Consequently, mitochondrial dysfunction exposes the liver to various forms of injury and attacks by ROS apoptic machineries that can lead to NAFLD.

Oxidative stress which has been reported to be strongly associated with the amount of fat in the liveris considered as the most important mechanism that causes hepatocyte damage. Long term oxidative stress stimulates the liver, which may lead to nonalcoholic steatohepatitis (NASH) and cirrhosis [51]. According to [41] oxidative

stress causes liver damage through the "two-hit" hypothesis. The produced reactive oxygen species (ROS) increase damage to oxidative phosphorylation uncoupling and cell membrane leading to a vicious cycle that aggravates liver inflammation. Xu *et al.* [52] further explained that ROS formed by oxidative stress secondary to high fat accumulation can combine with biological membrane phospholipids, enzymes, membrane receptor polyunsaturated fatty acid side chains, and macromolecules like nucleic acid, resulting in lipid peroxidation. The resulting lipid peroxides can increase endogenous ROS and toxicity which inhibit the antioxidant system. Lipid peroxidation can promote the synthesis and release of malondialdehyde (MDA) and B-hydroxylated nonene. Oxidative stress, lipid peroxidation, and mitochondrial damage further increase ROS/RNS production and accelerate and worsen fatty degeneration resulting in NASH and fibrosis.

MOLECULAR BASIS OF AUTOIMMUNE- INDUCED HEPATITIS

Autoimmune hepatitis (AIH)is a corticosteroid-responsive liver disease arising as a result of immunogenetic and environmental risk factors [53]. It is considered a rare chronic liver disease of unknown cause predominantly affecting women, but occurring in children and adults of all ages [30]. It is characterized by continuing hepatocellular inflammation and necrosis, which generally progresses to cirrhosis [1] hypergammaglobulinemia and a variety of autoantibodies [30], slight increase in serum transaminase predominantly alkaline phosphatase[54] and is always associated with other autoimmune conditions such as coeliac disease, vasculitis, and autoimmune thyroid disease [55].Autoimmune hepatitis AIH is classified into 3 types according to serum autoantibody. Type 1 is most commonly characterized by anti-smooth muscle antibody (SMA) and/ or anti-nuclear antibody (ANA) positive. Type 2, characterized by anti-liver and kidney microsomal antibody (LKM-1) positive, is rare in adults. Type 3 is characterized by anti-soluble liver antigen antibody/anti-hepatopancreatic antibody (SLA/LP) positive [30]. Though the pathogenesis of AIH is not clear, genetic susceptibility is considered to be the main factor. Nevertheless, AIH patients are always proved to lack immunoregulatory function, which is newly considered to be the cardinal cause of AIH [30].

Environment, drugs, infection and other factors caninduce susceptible genes (human leukocyte antigens (HLA)-encoding genes) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) +49 A/G polymorphism) in carriers which can predispose them to AIH [55]. Example, there has been a claim that the haplotype of HLA is more closely involved in susceptibility to AIH and more strongly modifies the clinical manifestations of type 1 AIH [56]. The association between the HLA-DR or HLA-DRB1 allele and AIH is widely accepted. Other studies also show that another locus of HLA (A, B, C, or DQ) may be closely associated with AIH [30].Autoimmune hepatitis AIH is characterized by a lack of immune tolerance (a state of specific unresponsiveness that occurs when immunologically active cells are exposed to antigenic substances) to hepatocyte antigens and eventually leads to liver parenchymal cell damage mediated by auto-reactive T cells [57].Also, [30] mentioned that AIH is considered to be initiated by an immunological reaction against autologous liver antigens.

Combination of genetic predisposition, environmental stimulus (e.g., microbial products, drugs metabolites, and associated haptens), and an imbalance in immunological regulatory mechanisms leads to loss of tolerance during AIH. The resultant effect of the loss of tolerance leads to cytotoxic T cell–mediated hepatocellular injury with important participation of multiple T cell subsets and B cells [58]. Cytotoxic T cells (CTL) can be divided into

CD4 CTL and CD8 CTL, which can result in liver injury. It is generally believed that the molecular mechanism of CTL-mediated target cytotoxicity occurs in the following ways:

The perforation-based degranulation pathway, rapidly inducing target cell death, which mainly refers to CD8 CTL; another pathway is the Fas-mediated hepatocellular apoptosis, the Fas ligand (FasL) on the CTL binding with the target cell-associated Fas antigen induced apoptosis of target cells, which mainly refers to CD4 CTL [59]. Fas-mediated hepatocellular apoptosis may also be one of the important mechanisms of hepatocyte injury in the pathogenesis of AIH [60]. Immunohistochemical studies showed that Fas was expressed on hepatocytes in patients with AIH, and Fas expression levels can respond to the severity of autoimmune hepatitis. At the same time, the studies have found potentially important target antigens, such as the pathogenesis of AIH cytochrome P450 2D6 and anti-sialoglycoprotein receptor (ASGPR), which both express on the liver cell surface [30].

Antibody-dependent cell-mediated cytotoxicity (ADCC) was also found to play role in AIH. The course of action in AIH referring to ADCC is that autoimmune liver disease plasma cells secrete a large number of anti-liver cell antigen autoantibodies with the synergistic effect of T cells, which interact with the protein components of the liver cell membrane to form immune complexes, then natural killer cells (NK cells) correspond to the binding of IgG Fc fragment bound to target cells by its surface receptors, and after that NK cells activate the releasing of perforin, granzyme and other cytotoxic substances to kill target cells [30].

MOLECULAR BASIS OF TOXIN INDUCED HEPATITIS
Organic and Inorganic Toxins

Hepatotoxicants are exogenous compounds of clinical relevance and may include overdoses of certain medicinal drugs, industrial chemicals, natural chemicals like microcystins, herbal remedies and dietary supplements that elicit damage to the liver at varying degree which are sometimes concentration dependent [14].Hepatotoxins can be of organic origin of which the most important ones can include mycotoxins or inorganic sources which can include heavy metals, industrial chemicals and agrochemicals. Hepatotoxicity can be elicited by either parent compound or toxic metabolite, differential expression of enzymes and concentration gradient of cofactors in blood across the acinus [61]. Toxins generally follow the mechanism of inflammation, dysfunction of cytochrome P450, mitochondrial dysfunction and oxidative stress to elicit their toxic effects [62]. According to [14], the hepatotoxic effects of chemical agents (toxins) may involve different mechanisms of cytolethality which can have either direct effect on organelles like mitochondria, endoplasmic reticulum, the cytoskeleton, microtubules and nucleus or indirect effect on cellular organelles through the activation and inhibition of signalling kinases, transcription factors and gene-expression profiles. The resultant intracellular stress may manifest as death caused by either cell shrinkage and nuclear disassembly (apoptosis) or swelling and lysis (necrosis), hence liver injury.

Hepatotoxicants can attack directly certain critical cellular targets like plasma membrane, mitochondria, endoplasmic reticulum, nucleus and lysosomes thus disrupting their activity. Some chemicals and metal ions bind to mitochondrial membranes and enzymes, disrupting energy metabolism and cellular respiration [61], while others act as direct inhibitors and uncouplers of mitochondrial electron transport. [63] Studies on organophosphorus hepatotoxicity was found to cause hepatocellular damage through these mechanisms as reported by [64]. According to [65], tissue damage stimulates hepatic Kupffer cells to release inflammatory cytokines, IL-1β, IL-6, and INF-γ. Inflammatory cytokines affect the function

of hepatocytes and stellate cells, leading to various hepatic damaging effects, e.g., hepatitis, steatosis, or apoptotic cell death.

The mushroom toxin, phalloidin also causes increase in plasma membrane permeability by binding to actin and disrupting the cell cytoskeleton [66]. Glutathione provides an efficient detoxification pathway for most electrophilic reactive metabolites. However excess substrates and their metabolites beyond conjugation capacity of glutathione can lead to its depletion thus rendering cells more susceptible to the toxic effects of chemicals [14].

High prooxidant to antioxidant ratio which causes oxidative stress causes hepatotoxicity which can lead to death of hepatocytes through increased cell membrane permeability, decreased cell membrane fluidity, inactivation of membrane proteins and loss of polarity of mitochondrial membranes thereby impairing cell function [67]. Halogenated hydrocarbons, hydroperoxides, acrylonitrile, cadmium, iodoacetamide, chloroacetamide and sodium vanadate are toxins reported to exhibit hepatotoxicity through this mechanism [14]. Based on the recent findings by [68], aflatoxin AF which is a mycotoxin exhibits its hepatotoxicity through oxidative stress. For instance, the toxic effects of AFB1 against the liver and other organs were found to be closely related to its metabolic activation into the free radical AFB1-exo-8,9-epoxide (AFBO) by cytochrome P450 (CYP450) enzymes [69] and associated formation of reactive oxygen species (ROS) including hydroxyl radical (HO.), per hydroxyl radical (HOO-) and superoxide anion [70]which subsequently overwhelm the limited antioxidant capacity of the system. The oxidative stress generated by this process results in the damage of biological molecules including lipids, proteins and DNA in cellular systems [71].Badr, 2020 [65] also reported that malathion; an organophosphorus pesticide follows the same mechanism in inducing hepatotoxicity.

In another study, [72] reported that a non-selective herbicide called paraquat follows similar pattern in its mechanism of hepatotoxicity. Reactive oxygen species ROS induced mitochondrial damage is known to cause uncoupling of mitochondrial oxidative phosphorylation and the associated reduction in mitochondrial membrane potential which leads to activation of cytochrome C that modulates Bcl2/Bax gene expression and activate caspase 9 and caspase 3, that result in cell death [68]. As reported by [14] lead and arsenic were found to generate reactive oxygen species, stimulation of lipid peroxidation and decreased antioxidant defense system which are the possible mechanisms of their hepatotoxicity.

Calcium is involved in a wide variety of critical physiological functions and its homeostasis is very precisely regulated in the cell by an active membrane-associated calcium and magnesium effluxing adenosine triphosphatase (ATPase) enzyme system which is an important potential target for toxicants [14]. Cytosolic free calcium is maintained at relatively lower concentration. However, some chemicals like quinines, peroxides, acetaminophen, iron and cadmium disrupt calcium homeostasis [73]. Non-specific increases in permeability of the plasma membrane, mitochondrial membrane and membranes of smooth endoplasmic reticulum lead to disruption of calcium homeostasis by increasing intracellular calcium. Also decline in available NADPH, a cofactor required by calcium pump may also disrupt calcium homeostasis. The disruption of calcium homeostasis may result in the activation of many membrane damaging enzymes like ATPases, phospholipases, proteases and endonucleases, disruption of mitochondrial metabolism and ATP synthesis and damage of microfilaments used to support cell structure hence liver injury [14].

Some chemical toxins have also been found to cause hepatotoxicity through the mediation of hepatosteatosis. An

organophosphorus chemical e.g. malathion has been reported to follow this mechanism by causing changes in glucose, protein, and lipid metabolism [65].

CONCLUSION

Non-infectious hepatitis is indeed on the rise globally due to industrialization and lifestyle changes. Many of the causes and pathological mechanisms of this ailment still remain to be understood despite the efforts continuously channelled towards the understanding and management of the disease. However, research is a loose ended and continuous process hence proper understanding of present findings will provide a background for further studies in a bid to unravel some of the mysteries in non-infectious hepatitis hence a more efficient and effective approach of treatment/ management .

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