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Evaluating Hepatotoxicity: Insights and Implications from Recent Research

Manish Kumar Kaushik[1], Monika Singh *[2], Moumita Barman[3]
[1]Research Scholar, Pharmacology, ITS College of Pharmacy, Murad Nagar
[2]Assistant Professor, Pharmacology, ITS College of Pharmacy, Murad Nagar
[3]Associate Professor, Pharmaceutics, ITS College of Pharmacy, Murad Nagar

Corresponding Author:
Email Id: monikas@its.edu.in

ABSTRACT

Hepatotoxicity is a harmful pharmacological reaction that might be uncommon but severe; it is the damage or harm to the liver caused by exposure to medications. Due to an increase in alanine aminotransferase and alkaline phosphatase levels over the upper limit of normal, the liver damage might be classified as hepatocellular, cholestatic, or mixed. The risk factors include lifestyle, age, gender, and alcohol use, concurrent drug use, prior or underlying liver disease, genetics, and environmental factors. The symptoms of liver toxicity are often monitored with the use of nonspecific indicators such as fever, jaundice, stomach discomfort, diarrhea, vomiting, pruritus, and rash. The review provides a brief explanation of liver-related injuries and the function of antioxidants in oxidative stress. A very uncommon hepatic disorder known as drug-induced liver damage (DILI) is brought on by the use of prescription pharmaceuticals, illicit substances, herbal remedies, or nutritional supplements. It is thought that a combination of genetic and environmental risk factors alters drug metabolism and/or excretion, causing a series of cellular events in susceptible individuals, such as the formation of oxidative stress, apoptosis/necrosis, haptenization, activation of the immune system, and a failure to adapt.

Key Words: *Hepatotoxicity, Metabolism, Gluconeogenesis, Liver toxicity.*

INTRODUCTION

About the Liver Toxicity

Herbal hepatotoxicity or herb induced liver injury (HILI) is causally related to natural products consumed by humans. Usually, these herbs are avoided by animals due to protective mechanisms as nicely described two decades ago.[1,2] Herbs synthesize a broad spectrum of chemicals with beneficial properties when used in appropriate amounts and with toxic features when consumed in excess. When herbivorous animals encounter these plants, they normally leave these herbs due to their often unpleasant, strong, bitter, or fetid taste. The same plants are collected by humans for herbal preparations. Herbs are used either in their original forms as teas and food additives, or are manufactured into herbal products like herbal drugs and herbal supplements. Though, erroneously, herbs and herbal products were considered safe for a long time, there is now growing evidence that herbs may cause adverse reactions of variable severity involving numerous organs including the liver[3].

Role of Liver

The mechanisms by which the liver maintains a constant supply of oxidizable substrates, which provide energy to the body as a whole. During feeding, the liver builds up energy stores in the form of glycogen and triglyceride, the latter being exported to adipose tissue.

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During fasting, it releases glucose and ketone bodies. Glucose is formed by degradation of glycogen and by gluconeogenesis from gluconeogenic amino acids provided by muscle. Ketone bodies are produced from fatty acids, released by adipose tissue, and from ketogenic amino acids. The major signals which control the transition between the fed and the fasted state are glucose, insulin and glucagon. These influence directly or indirectly the enzymes which regulate liver carbohydrate and fatty acid metabolism and thereby orient metabolic fluxes towards either energy storage or substrate release. In the fed state, the liver utilizes the energy generated by glucose oxidation to synthesize triglycerides. In the fasted state it utilizes that produced by fl-oxidation of fatty acids to synthesize glucose. The mechanisms whereby a number of inborn errors of glycogen metabolism, of gluconeogenesis and of ketogenesis cause hypoglycaemia[4].

The main metabolic fuels of the human body are glucose, fatty acids and ketone bodies. Its principal energy stores are liver glycogen, adipose tissue triglyceride and muscle protein. In the metabolic homeostasis of the body as a whole, the liver occupies a central position. Indeed, besides building up glycogen in its own cells, the liver plays an essential r61e in the synthesis of adipose tissue triglyceride, by producing very-low-density lipoproteins, and of muscle protein, by synthesizing non-essential amino acids. Furthermore, the liver furnishes oxidizable substrates, not only to meet its own needs, but also to cover those of other tissues. Glucose, the only fuel which red blood cells can use and nearly the only one which the brain utilizes, is only synthesized by liver and, to a lesser extent, by kidney cortex. Ketone bodies which during prolonged fasting are a major fuel for heart and muscle, and also for brain, are exclusively formed by the liver.[5,6]

Epidemiology of Liver Toxicity

By virtue of its strategic location as the delta of the portal blood stream, the liver is massively exposed to drugs and other foreign compounds absorbed from the intestine. In the “first pass” of portal blood through the liver, the affinity and capacity of uptake, biotransformation, transport, and excretory processes determine how much drug enters the systemic circulation, its bioavailability. A common first step in the biotransformation of drugs is metabolism by the cytochrome P450 (CYP) hemoproteins[78].7 Drug metabolism, drug passaging, secretion of bile, and cell defenses are essential for survival of the organism, and all require metabolic energy. Hepatocytes have evolved to form a specialized type of epithelium, richly endowed with such metabolic prowess. They exhibit an adaptable and highly efficient repertoire of plasma membrane transporters to effectively eliminate foreign compounds, particularly conjugated or ionized molecules[910].

Hepatic uptake, biotransformation, intracellular transport, and excretion in bile are important processes that clear drugs from the body, terminate their pharmacological action, and prevent toxic accumulation. These processes are well understood in terms of their kinetic influence on drug distribution and elimination, but the exciting new advances involve discovery of the molecular events that mediate and integrate hepatic drug clearance. What has always been noteworthy, but poorly understood, is how the pathways of drug handling by the liver are regulated. For instance, levels and activities of CYP proteins may be induced 5-fold, and transcripts of CYP genes may change 50-fold after exposure to foreign compounds. The remarkable adaptability of this system has implications for the disposition and metabolism of particular drugs between individuals, and it carries the potential to explain individual susceptibility to drug-induced liver injury.[11]

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FACTOR AFFECTING DRUG INDUCED TOXICITY

Age

Older age is traditionally thought to be a risk factor for DIL. Drug-induced acute liver failure (DIALF) is commonly seen in relatively young population in India. As per documented epidemiological report the percentage of DILI is 8.7% in children ranging from 3 to 17 years.[12]

Gender

From the research studies it is clear that women are generally at higher risk for DILI and DIALF. Study report conducted in Japan and Sweden clearly suggests that women constitute 58% and 56% of all cases of DILI respectively.[13]

Concomitant medication

The interaction between drugs administered concomitantly is complex, challenging and complicates causality assessment. Drugs interaction may have reciprocal effect such that drug either increases or decreases the potential for hepatotoxicity.[14]

Nutrition

Nutritional deficiency may predispose to DILI as reported in patients with HIV, tuberculosis or alcoholism. This is largely due to the reduced hepatic glutathione in liver tissues of these patients[15]

Alcohol

Alcohol is believed to be one of the most important risk factors for DILI, but its exact role is not fully understood. Although, the chronic use of alcohol particularly with malnutrition depletes the glutathione stores, the exact link between alcoholism and liver injury is lacking[16]

Genetic Factors

Genetic polymorphism of enzymes and proteins linked to the metabolism of drugs are important predisposing factors in DILI. Individuals with slow acetylator status have increased incidence and severity of INH-induced hepatitis (Den Brinker et al., 2000). A recent study from New-Delhi, India demonstrated slow acetylator status is 71% in patients with tuberculosis DILI as compared to 45% without DILI[17]

Drug Dose and Varied Adverse Triggering Factors

As observed a strong dose response relationship exist between drug and hepatotoxicity. They further stated drugs administered >50mg doses of oral medications showed an enhanced risk of DILI. A variety of adverse stimuli may trigger liver injury, including a job that exposes person to other person's blood and body fluids, blood transfusion, body piercings, certain herbs and food supplements, certain medications (drugs), diabetes, heavy alcohol consumption, high blood triglycerides, use of shared needles for drug injection, obesity, tattoos, unprotected sex, xenobiotics or toxins, gamma radiations and oxidative stress. It is recognized that immune factors, such as autoimmune stimuli, virus or parasite infection, are the major causative factors of hepatic damage especially hepatitis[18].

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DRUG INDUCED DAMAGE

Rifampicin

Rifampicin therapy have an increased incidence of hepatitis. This has been postulated due to Rifampicin-induced cytochrome P450 enzyme-induction, causing an increased production of the toxic metabolites from acetyl hydrazine (AcHz)[19]. Rifampicin also increases the metabolism of INH to isonicotinic acid and hydrazine, both of which are hepatotoxic. The plasma half-life of AcHz (metabolite of INH) is shortened by Rifampicin and AcHz is quickly converted to its active metabolites by increasing the oxidative elimination rate of AcHz, which is related to the higher incidence of liver necrosis caused by INH and Rifampicin in combination. Rifampicin also interacts with antiretroviral drugs and affects the plasma levels of these drugs as well as risk of hepatotoxicity[20]

Isoniazid

Isoniazid hepatotoxicity is a common complication of antituberculosis therapy that ranges in severity from asymptomatic elevation of serum transaminases to hepatic failure requiring liver transplantation. This is not caused by high plasma Isoniazid levels but appears to represent an idiosyncratic response. INH is metabolized to monoacetyl hydrazine, which is further metabolized to a toxic product by cytochrome P450 leading to hepatotoxicity.[21] Human genetic studies have shown that cytochrome P4502E1 (CYP2E1) is involved in anti-tubercular drug hepatotoxicity[22] The CYP2E1 c1/c1 genotype is associated with a higher CYP2E1 activity and may lead to a higher production of hepatotoxins. Rat studies showed that Isoniazid and Hydrazine induce CYP2E1 activity[23] . Isoniazid has an inhibiting effect on CYP1A2, 2A6, 2C19 and 3A4 activity. CYP1A2 is suggested to be involved in hydrazine detoxification. Isoniazid can induce its own toxicity, possibly by the induction or inhibition of these enzymes[24]

Acetoaminophen

Acetaminophen is sometimes referred to as N-acetylp-aminophenol [APAP] or paracetamol. A trustworthy and effective antipyretic and analgesic medication is advised. The suggested dosage of APAP stimulation is 325–650 mg every 4-6 hours for adults, with a maximum of 4 grams per day, and 10-15mg/kg every 4-6 hours for children, with a maximum of 50–75 mg/kg. When administered therapeutically, APAP is metabolized predominantly in the liver (5–9%) by the Cytochrome P-450 enzyme system into the reactive metabolite N-acetyl-p-benzo-quinoneimine (NAPQI). However, 80–90% of the compound is metabolized via the phase II metabolic pathway (glucuronidation and sulfation), wherein UDP-glucuronosyl transferases (UGT) and sulfotransferases (SULT) catalyze the APA-produced glutathione (GSH) conjugate[25]. These compounds are non-toxic and are excreted through urine. However, consuming APAP for prolonged periods of time might be dangerous. Due to the overproduction of NAPQI metabolite, which results in lipid peroxidation, it may attach to cellular proteins and create protein adducts, which can induce cell necrosis and the loss of metabolic energy (adenosine triphosphate, or ATP). The classic example of a direct liver injury is the APAP hepatotoxicity, which can harm the livers of experimental animals as well as humans in both acute and severe ways[26]. APAP hepatotoxicity is presently the leading cause of acute liver failure globally and is linked to a considerable number of fatalities

Pyrogallol

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Pyrogallol (benzene-1, 2, 3-triol), a naturally occurring polyphenol of plant origin, possesses antifungal and anti-psoriatic effects. It is also polyphenolic tannin, having a structure that facilitates interactions with hydrophobic and hydrogen-bonding molecules [27]. Thus, pyrogallol may interact with various ions and biomolecules such as metal ions, proteins, and polysaccharides. Pyrogallol is a frequent element in hair dyes and development solutions for pictures due to its helpful features in the industry. The understanding that tannins such as pyrogallol found in eucalyptus leaf leachate may enter water bodies and combine with iron to create complexes is the basis for the toxicity theory[28]. Pyrogallol's autoxidation ability can have negative consequences on watery habitats, including a decrease in oxygen, changes to the water's pH and color, and temporary changes to fish behavior.[29]

Superoxide anions, a kind of free radical that can cause oxidative damage and toxicity to several organ systems, are produced when pyrogallocallol is administered. Studies suggest that pyrogallol can trigger apoptosis in a number of cell types, including fibroblasts, endothelial cells, and malignant cells. Moreover, histological damage has been noted, which includes hepatotoxicity linked to oxidative stress and the deterioration of aquatic species' gill filaments. In addition, exposure to pyrogallol changed the liver's microstructure and increased bilirubin and blood transaminase levels[30]. As a result, in animals exposed to pyrogallol, evaluating blood biochemical markers and histological indications are helpful methods as biomarkers of liver and spleen damage.[31]

Diclofenac

A phenylacetic acid derivative, diclofenac (dye kloe' fen ak) is a member of the acetic acid class of nonsteroidal anti-inflammatory drugs (NSAIDs), which also includes indomethacin, etodolac, ketorolac, nabumetone, tolmetin, and sulindac. As with other nonsteroidal anti-inflammatory drugs (NSAIDs), diclofenac works by blocking the activity of cellular cyclooxygenases (Cox-1 and Cox-2). This leads to a reduction in the synthesis of pro-inflammatory prostaglandin, prostacyclin, and thromboxane molecules, which are crucial mediators of pain and inflammation[32]. Diclofenac has antipyretic, anti-inflammatory, and analgesic properties. Topical diclofenac formulations (solutions, gels, creams, and patches) have only been linked to a negligibly low risk of elevated blood enzymes (usually less than 1%) which may not be any higher than what happens when a vehicle or placebo is applied[33]. On the other hand, topical diclofenac product labels discuss the potential for liver damage, and at least one case of clearly visible liver damage linked to the drug has been documented in the literature. However, it must be quite unusual for topical versions of diclofenac to cause clinically noticeable liver damage.[34]

The hepatotoxicity caused by diclofenac is usually linked to an acute histology resembling hepatitis, along with necrosis, which can be especially noticeable in zone 3 (centralized). There is generally localized necrosis and inflammation, although with severe cases the damage might be confluent or submassive[35]. Chronic hepatitis-like damage with predominance of portal inflammation, interface hepatitis and fibrosis can be detected, particularly in instances with longer latency and more extended course. Hepatocellular cholestatic damage (cholestatic hepatitis) in a minority of patients exhibited mixed inflammation to differing degrees.[36]

A variety of factors may contribute to modest blood aminotransferase increases and substantial liver disease; the process of diclofenac-induced liver injury appears to be complex. The quick and acute recurrence of harm, even years after the first exposure and

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injury, suggests an immuno-allergic component. Genetic research has indicated a connection to allelic variants of the diclofenac metabolism, conjugation, and excretion genes UGT 2B7, CYP 2C8, and ABC C2.[37]

Statins

it is well documented that statins increase liver enzymes, risk of myopathy, and risk of diabetes mellitus (DM). The two most frequent side effects of statins are myopathy and hepatotoxicity.[38] Statins can cause hepatotoxicity and myopathy, and the likelihood of these side effects increases when the drug is used: i. at maximum dosages; ii. in combination with other lipid-lowering medications like fibrates (drug-drug interaction); iii. in conjunction with medications that use the same enzymatic pathway, like some cytochrome P450 enzymes; iv. by elderly patients and patients with significant hepatic and/or renal dysfunction.[39] Higher dosages of statins were associated with liver damage, which was not found at therapeutic levels, according to animal trials. Simvastatin and lovastatin at high dosages in rabbits induced hepatic cell necrosis in guinea pigs. Since the ingestion of mevalonate or its downstream metabolites may be the cause of the harm, mevalonate reinforcement can prevent or reverse the liver injury in these animals.[40] One of the main theories explaining the mechanism of statin-induced hepatotoxicity is mitochondrial dysfunction. In vitro studies demonstrated the dose- and time-dependent suppression of mitochondrial activity by statins. The results of the mitochondrial toxicity experiment show a substantial rise in mitochondrial superoxide following statin administration.[41] The fact that statins stimulate apoptotic cell death is a significant contributing factor to statin-induced hepatotoxicity. The processes responsible for hepatotoxicity include the depolarization of the mitochondrial membrane, the release of Ca+2, and the suppression of the respiratory chain (complex I and III).[42]

Drugs are broken down by the cytochrome P450 enzymes in the liver. One subfamily of these enzymes is the super family of monooxygenases. Their members may play a crucial role in the xenobiotics' catabolism[43]. Both mitochondria and cytochrome P450-dependent metabolism function as pathways for the production of reactive oxygen species (ROS) and play a role in cell death processes. When statins are used, hepatocytes release a large quantity of reactive oxygen species. They induce lipid peroxidation, which lowers the potential of the mitochondrial membrane and increases cytotoxicity[44].

Mechanism Behind Hepatotoxicity

Drug Metabolizing Enzymes

The term "drug-metabolizing enzymes" refers to a class of enzymes that includes several different enzymes, such as NADPH-cytochrome P450 reductase, cytochrome P450, and cytochrome B5. The hepatic cytochrome P450s (Cyp) are a multigene family of enzymes that are essential for the metabolism of several medicines and xenobiotics[45]. The activation and inhibition of each cytochrome isozyme in response to external substances varies. Cyp 1A1, for instance, exhibits heightened activity in relation to polycyclic aromatic hydrocarbons (PAHs), converting them into reactive intermediates that subsequently form a covalent bond with DNA, a crucial step in the commencement of carcinogenesis[46]. Similarly, amides and aromatic amines are among the bladder carcinogens that Cyp 1A2 activates.

Furthermore, certain cytochrome P450 isozymes, such as Cyp 3A and 2E1, can convert naturally existing carcinogens, such as aflatoxin B1, into highly mutagenic and carcinogenic substances by activating N-nitrosamines[47]. The stimulation of cytochrome P450 isozymes is associated with the carcinogenic potency of PAHs and other carcinogens as well as the

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degree of binding of their final metabolites to proteins and DN[48]. Chemical carcinogens are rendered less dangerous or inactive by phase II drug-metabolizing enzymes such glutathione S-transferase, aryl sulfatase, and UDP-glucuronyl transferase[49].

By altering the activity of phases I and II drug-metabolizing enzymes, many medications alter the pace at which carcinogens activate or detoxify. The equilibrium between the activation and detoxification processes is determined by the chemical structure of the agents and is influenced by a variety of factors, including age, nutrition, sex, endocrine state, genetic background, and the presence of additional substances.[50] It is crucial to understand that the enzymes engaged in the metabolism of carcinogens also participate in the metabolism of a range of substrates[51]. As a result, the presence and number of other compounds may alter in response to the arrival of certain xenobiotics[52]. The book has covered the processes underlying the alteration of drug-metabolizing enzyme activity as well as their function in the activation and detoxification of xenobiotics and carcinogens[53].

Phase 1

The metabolism of vitamins, endobiotics (fatty acid derivatives), endogenous steroid hormones, and a variety of drugs and xenobiotics is aided by the heme-containing, mixed function oxidase enzymes known as cytochrome P450 (CYP)[54]. Numerous endogenous and exogenous substances can eas ily induce CYP. [55]When xenobiotics are oxidized by CYP, a highly electrophilic intermediate is produced that can bind to essential cell macromolecules including membrane proteins that control Ca++ homeostasis and contain thiols[56].Cell death may be regularly promoted by the activation of elevated intracellular calcium[57]. Lipid peroxidation caused by free radical intermediates produced by CYP-mediated reduction of halogenated hydrocarbons, such as carbon tetrachloride or halothane, can directly damage cell layers[58]. Different nuclear receptors govern phase I reactions, which are mediated by different isoforms of CYPs and catalyzed by different drugs and xenobiotics[59].[60] The process of phase I enzyme impelling by microsomal inducers involves the activation of transcription factors, such as constitutive androstane receptor (CAR), aryl hydrocarbon receptor (AhR), pregnane X receptor (PXR), and peroxisome proliferator-actuated receptor α (PPARα)[61]. It has been observed that different CYP isoforms have a role in drug metabolism and, therefore, bioactivation. Of the already marketed therapeutic medicines, 50%, 25%, and 20% of their metabolic activation is attributed to the CYP3A, CYP2D, and CYP2C subfamilies, respectively[62]. The main CYP isoforms implicated in rat drug metabolism are CYP1A2, 2C7, 2C11, 2D2, 2E1, 2B1/2, and 3A1/2. The role of 1A2 and CYP2E1 in the acetaminophen and pyrogallol activation has been established in animal models.[63]

Phase 2

Phase II enzyme detoxification reduces the impact of bio-molecular adducts on cellular homeostasis by removing reactive intermediates from cellular surroundings[64]. Phase II enzymes are primarily responsible for the reduction of toxicity and enhancement of water solubility through the conjugation of activated pro-toxicants with endogenous biomolecules such as glucuronic acid or GSH[65]. An essential Phase II enzyme called glutathione-S-transferases (GST) catalyzes the conjugation of glutathione's -SH moiety to xenobiotics, which neutralizes the electrophilic sites and increases the products' water solubility[66]. This action starts the detoxification process. It is believed that glutathione conjugates undergo further metabolism that results in mercapturic acid by cleaving the glutamate and glycine residues and then acetylating the free amino groups that remain on the cysteinyl residue[67].[68]
Herbal medication

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Silymarin

Milk thistle seed extract, silymarin, has been used for generations to treat liver ailments. According to preclinical research, silymarin can lessen oxidative stress and the cytotoxicity that follows, sparing intact liver cells or cells that have not yet sustained irreversible damage[69]. To increase silymarin's oral bioavailability, a new formulation called Eurosil 85® was created. This formulation has been employed in the majority of silymarin clinical trials. Silymarin inhibits enzymes linked to the onset of fibrosis, cirrhosis, and cellular damage by acting as a scavenger of free radicals. Patients with alcoholic or non-alcoholic fatty liver disease, including those with cirrhosis, showed these hepatoprotective benefits in clinical trials[70]. A substantial decrease in liver-related mortality was linked to silymarin therapy in a pooled analysis of studies including patients with cirrhosis. Furthermore, silymarin was shown to be able to improve glycemic indices in individuals with alcoholic cirrhosis and diabetes[71]. Silymarin has also been used to treat patients with drug-induced liver damage with effectiveness. With a low frequency of adverse events and no documented significant adverse events or treatment-related fatalities in clinical studies, silymarin is typically extremely well tolerated[72]. When the liver's capacity for regeneration is still high and oxidative stress—the root cause of cytotoxicity—can be eliminated, silymarin therapy should be started as soon as possible in patients with fatty liver disease and other unique liver disease manifestations, such as acute liver failure, in order to optimize benefit[73]. Silymarin, an extract from milk thistle, is a complex combination of chemicals obtained from plants, primarily flavonolignans, flavonoids (quercetin, taxifolin), and polyphenolic polymers[74] . These substances have several additional physiological characteristics and are also known to be antioxidants [75]. The most common and physiologically active of the four major flavonolignan isomers in silymarin, silibinin (also known as silybin), isosilibinin, silichristin, and silidianin. Silibin makes up around 50–60% of the silymarin complex, while the other flavonolignan isomers—silichristin (20%), silidianin (10%), and isosilibinin (~5%)—make up the remaining about 35%. With a molecular weight of 482.44 g/mol and a formula of C25H22O10, silibinin is a polyphenolic flavonoid antioxidant . silibinin is really a combination of two diastereomers, silibinin A and silibinin B, in a roughly equimolar ratio . In the liver, it proceeds through phases I and II of biotransformation. Phase II conjugation reactions have been reported, resulting in the synthesis of derivatives of glucuronide and glucuronide sulfate.[7677]

Resevetrol

Naturally existing polyphenol resveratrol has a wide range of positive health effects, such as anti-aging, anti-inflammatory, antioxidant, and cardioprotective properties. Plants that are being attacked by fungus or bacteria generate the phytoalexin resveratrol[78]. Red grapes, eucalyptus, spruce, blueberries, mulberries, peanuts, and giant knotweed are just a few of the numerous plants and foods that contain resveratrol[79]. A plentiful source of it is red wine as well. Trihydroxystilbene trans-3,5,4′ is its chemical name. Because of its strong antioxidant content, it may have anticarcinogenic, antidiabetic, neuprotective, and cardioprotective effects. Primary rat hepatocyte cultures were treated to different doses of resveratrol (25, 50, and 75 μM) and 300 μM tBHP in order to examine the protective antioxidant effect of resveratrol. The medium's release of LDH was used to measure necrosis. The necrosis caused by tBHP was reduced by resveratrol[80]. It was also successful in getting rid of ROS. The findings demonstrate that resveratrol shields primary rat hepatocytes in culture against cell death brought on by oxidative stress. to clarify the chemical mechanism via which resveratrol shields liver cells from damage caused by oxidative stress The study focused on the activation of the Nrf2 transcription factor, which controls the production of phase II detoxifying enzymes and antioxidants[81]. Hepatocytes in culture subjected to oxidative stress

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were significantly protected by resveratrol pretreatment, which also increased the activities of GST, SOD, GPx, NADPH quinone oxidoreductase, and catalase. Resveratrol causes Nrf2 to translocate to the nucleus and raises its level. Additionally, it raises the Nrf2 mRNA concentration. These findings imply that resveratrol may improve the hepatic cells' antioxidant state and may be a helpful medication for shielding the liver cells from harm brought on by oxidative stress. the impact of resveratrol's bioavailability from food sources on hepatic LPO brought on by CCl_4[82]. Resveratrol (3 mg/kg) was given intraperitoneally to ten rats for a duration of 14 days, using an extract from grape stalks. Following one week, CCl_4 was used to induce hepatic LPO. The resveratrol content was assessed by collecting serum and liver samples at various time intervals. Measuring liver MDA served as an indicator of oxidative stress. After 14 days, resveratrol was shown to have significantly accumulated in the liver. Treatment with resveratrol decreased the rise in MDA liver levels caused by CCl_4 injection after one week by 63%. Thus, it was shown that dietary resveratrol consumption produced a time-dose-dependent hepatic accumulation that was able to prevent CCl_4-induced liver LPO, indicating resveratrol's hepatoprotective qualities. It was discovered that resveratrol (10 mg/kg) inhibited the hepatotoxic effects of pyrogallol (40 mg/kg). Resveratrol inhibited the rise in ALT, AST, bilirubin, LPO, and CYP2E1 and CYP1A2 catalytic activity that was induced by pyrogallol.[838485]

Curcumin

The popular herbal substance turmeric (tur mer' ik) is made from the roots of Curcuma longa, a perennial plant native to India that is found across Southern Asia and Central America and member of the ginger family (Zingiberaceae)[86]. Turmeric rhizome extracts contain volatile oils and curcuminoids, which are typically referred to as curcumin and include curcumin, demethoxycurcumin, and other compounds.[87] These compounds are thought to be the active anti-inflammatory ingredients in turmeric. It's believed that curcumin and turmeric limit the production of leukotrienes, which in turn has anti-inflammatory properties. It has also been shown that curcumin has antineoplastic properties, possibly through suppression of intracellular kinases[88]. Traditional Indian (Ayurvedic) medicine uses turmeric to cure a variety of ailments, such as indigestion,upper respirstory infection and liver disease. Notably, strategies for boosting piperine (black pepper) or nanoparticle delivery techniques to boost absorption have been developed in order to improve curcumin's bioavailability[89]. These high bioavailability turmeric forms were later associated with several liver damage cases and suggested as a potential cause of acute hepatitis with jaundice epidemics in Italy. More recently, the clinical characteristics of the liver damage linked to high bioavailable forms of turmeric have been clarified.[90] Though it usually takes one to three months, the latency period before liver damage manifests itself can range from a few weeks to up to eight months. The onset is gradual, starting with jaundice and dark urine and progressing to exhaustion, nausea, and poor appetite. There is either no rash or a slight fever. When laboratory testing is first performed, serum aminotransferase levels are usually significantly elevated (frequently > 1000 U/L), but alkaline phosphatase levels are only slightly elevated. Continue using the chemical and you get jaundice.[91] The clinical condition and histological findings might mimic autoimmune hepatitis, even though there are no obvious symptoms of hypersensitivity. Many individuals also acquire autoantibodies[92].

Ginkgo

The popular herbal remedy ginkgo (ging' koe) is made from the leaves and seeds of the Ginkgo biloba tree, which is considered a "living fossil" as it is the sole surviving member of a major order of plants that existed more than 200 million years ago (Ginkgoales)[93]. Although

it originated in central China, ginkgo has been brought to other countries. The Chinese term for "silver apricot," which refers to the fruit of the tree, is approximated in Japanese and is where the name "ginkgo" originates.[94] For millennia, ginkgo leaf and seed extracts were utilized in traditional Chinese medicine to treat a wide range of ailments[95]. While ginkgolides and bilobalide are exclusive to this herb, ginkgo extracts contain a variety of other chemicals as well. Studies have demonstrated the antihistaminic, anti-inflammatory, and antioxidant properties of ginkgo extracts. [96]Sometimes liver damage, whether acute or chronic, is treated with ginkgo. Although gingko shows some degree of inhibition of cytochrome P450 activity in vitro, it doesn't seem to have much of an impact on drug metabolism at levels administered to humans.[97]

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