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REVIEW ARTICLE

AN OVERVIEW OF HEPATOTOXICITY CAUSED BY DRUGS AND THE PROTECTIVE ROLE OF ANTIOXIDANTS: NARRATIVE REVIEW

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Drug-induced hepatotoxicity (DIH) is a major contributor to hepatotoxicity and a frequent cause of drug discontinuation or withdrawal by regulators. It comes about due to the direct toxicity of medications on hepatocytes, which is usually affected by genetic, environmental, and immunological conditions. The liver which is the focal point of drug metabolism is especially prone to be damaged by the use of prescription as well as over the counter simple medicines the herbal supplements. Clinical features of DIH range between mild increased levels of liver enzymes to life-threatening liver failure and have required liver transplant in some cases. Hepatotoxicity mechanisms are complex, and they include oxidative stress, mitochondrial dysfunction, inflammation, and cell death. Antioxidants have demonstrated potential in preventing liver injury by suppressing ROS, or reactive oxygen species and mitigating oxidative injury. Different researchers indicate that antioxidants, such as vitamins E and C, polyphenols, and compounds found in plants have the potential to reduce the effect of hepatotoxicity. The review addresses the pathophysiology of DIH, Oxidative stress's part in liver damage and the possible protective effect of antioxidants to prevent or decrease hepatotoxicity. It also emphasizes the necessity of further studies in order to create the new antioxidant-based therapies to provide the liver protection to the patients who were subjected to hepatotoxic drugs.

Keywords: Drug-induced hepatotoxicity, oxidative stress, antioxidants, liver injury, hepatocytes, reactive oxygen species.

INTRODUCTION

The pharmaceutical research process has increasingly become more costly, with the estimated average expense for successful drug development exceeding US $1.7 billion [1]. A graph depicting the annual number of authorized drugs indicates a somewhat stable trend.One cause of the issue is the challenges associated with target validation in complicated disease areas and the heightened regulatory obstacles[2].

Approximately 10,000 to 25,000 different compounds are typically considered during the creation of a new medicine. What are the principal factors contributing to the attrition of lead compounds? Twenty-five years ago, a significant issue was insufficient pharmacokinetics in humans. This domain has advanced due to knowledge of + transporters, other enzymes, human cytochrome P450 (P450), and the development of predictive in vitro tests. On the other hand, toxicity problems are increasing as metabolic difficulties decrease. About one-third of attrition cases are caused by adverse events in humans and pre-clinical toxicity in animals. The percentage is significantly greater when non-scientific reasons (such as commercial and financial ones) are excluded. The crux of the matter is the squandered resources (both temporal and financial) on substances that present toxicity issues, ultimately resulting in their abandonment in the development process. The toxicity and safety evaluation procedure occurs at multiple stages in the drug discovery and development cycle. If a potentially harmful substance is not discontinued promptly, the resultant financial loss can equivalent to years of research and hundreds of millions of dollars. As such, earlier choices are important in the creation of new drugs, and the first choice needs to be correct. Most of the drug-related

toxicity issues will be covered by this assessment. Drug-induced toxicity: The principle of Paracelsus posits that all substances can be detrimental in elevated doses while being benign at minimal doses. [3] Here, the emphasis is on cases of toxicity and adverse effects at levels that considerably affect individuals using a prescription, rather than accidental drug overdoses. The strategy for reducing toxicity or creating substitute chemicals with lower risks will depend on the toxicity environment. The most frequent problems are liver damage and cardiovascular problems.

It is possible to classify things in several ways. Although others have suggested different but similar categories, this systematic classification was previously outlined [4]. The main prerequisite for noxiousness is on-target (or mechanism-based) toxicity. It may result from the drug's interface with similar target that produces the required pharmacological advantage [5]. The theory put forth is that the drug's biological function, which entails attaching to the target, is what causes both its positive and negative effects rather than competitive inhibition. It is challenging to manage this type of toxicity because every drug class created to treat the illness will show toxicity. The condition may need a change in the target [6]. Statins, however, provide an illustration of the alternative approach. Statins are hypercholesterolemic drugs since they all aim to inhibit the liver's 3-hydroxy-3-methylglutaryl CoA (HMG CoA) reductase. The detrimental effects of HMGCoA reductase inhibition in muscle and potentially other tissues are made clear by the anti-biosynthetic effect of statins, especially the suppression of protein geranylgeranylation. Statin distribution across tissues can be changed by a variety of transport proteins, and while on-target toxicity is a worry, inter-tissue dispersion can mitigate it [7].

Hypersensitivity and immunological responses constitute the second scenario of drug toxicity. Penicillin-related allergic responses have long been known to occur. The concept, which was primarily developed on the basis of Landsteiner's seminal work [8], holds that medications (or their byproducts) interact with bodily proteins (as haptens) to produce antibodies and immunity. Since the substance in question (penicillins) is not entirely stable, and this can covalently bind to proteins and result the production of antibodies.

The third example of medicine toxicity can be called off-target toxicity. The medicine’s interactions are +

not selective, which is the problem. Binding to the alternative target is the source of toxicity. We shouldn't be shocked that a medication isn't always entirely specific given our present state of knowledge of the difficulty of biological controlling networks and multi-gene families (like protein kinases).

Bioactivation is the fourth scenario of drug toxicity. Reactive chemicals, also known as reactive metabolites, are produced from several drugs. Despite being difficult to identify by methods, these chemicals change the proteins they can also react to the toxicity (see infra). According to a different view, important regulatory or other proteins undergo modifications that cause them to lose their functioning. The altered proteins may also cause immunological reactions, which would connect them to the second toxicity context. When drug candidates were discontinued, metabolic problems were found in 28% of cases, according to a study of Bristol-Myers Squibb's pharmaceuticals.

Idiosyncratic reactions fall into the fifth class of toxicity. Characteristic means "individual," and they are some of the unusual occurrences (1/103 to 1/104 persons) that are ill-perceived. Since few of these animal models can be very predictive, these kinds of reactions are exceedingly problematic. Due to their low incidence, these opposing events are complex to be found even in large clinical tests. However, even a 1/104 incidence can result in hundreds of issues with extensively used medicines, where millions of prescriptions can be found. The difficulty of predicting safety issues is influenced by the toxicity environment.

Drug induce Hepatotoxicity:

The metabolism and excretion of a significant percentage of medications depend heavily on the liver. Drug metabolizing enzymes (DMEs) help the liver detoxify medications and xenobiotics, which is crucial for preserving homeostasis [9]. Changes in the dynamic equilibrium of metabolic processes brought about by changes in homeostatic status lead to the generation of reactive oxygen species (ROS), which subsequently induce organ malfunction and oxidative stress [10]. Microbial metabolites, specific drug combinations or dosages, and environmental toxicants are the leading causes of illness and mortality globally [11]. Drug consumption, anabolism, and excretion establish a dynamic equilibrium to achieve homeostasis. Phase I and Phase II enzymes are essential for the metabolism and detoxification of a number of medications and xenobiotics [12]. Enzymes

that metabolize xenobiotics must accurately control the metabolism of medications or xenobiotics in order to maintain dynamic homeostasis. An imbalance in the functions of these enzymes eventually results in an equilibrium shift that favors the production of free radicals, which can then bind to proteins to alter their activities, lipids to damage membranes, and macromolecules like DNA to induce mutations [13]. Often, hepatotoxic drugs and liver-damaging solvents are combined to form reactive intermediates. Medication side effects can include cholestasis (with or without inflammation), acute reactions (including liver necrosis), and other reactions; nevertheless, some drugs can result in tumor formation and irreversible damage. This study has looked into the medication's hepatotoxicity, possible contributing factors, mechanism of action, and prevention measures .

Numerous factors increase an individual's vulnerability to a potentially hepatotoxic substance. The danger of drug-induced hepatotoxicity can be influenced by a number of factors, including age, sex, lifestyle, nutritional status, genetic factors, dosage, and length of drug administration. Negative medication reactions are more common in people with comorbid diseases such rheumatoid arthritis, systemic lupus erythematosus, hepatitis C, and human immune-insufficiency virus. Drug composition and drug-drug interactions may increase the risk of drug-induced hepatotoxicity. For instance, certain medications, such as phenobarbital, that interact with nuclear receptors or include nitro-aromatic components may be hazardous to particular organs or may make other medications more toxic [14].

Drugs induced damage:

Pharmaceuticals like acetaminophen and idiosyncratic reactions from other medications are the main causes of the increasing annual frequency of acute liver failures in the United States [15]. Two to five percent of jaundice cases, and as well, more than ten percent of severe cases of acute hepatitis are as a result of drug-induced adverse effects, which have led to the removal of many medications and substances from the market. Epidemiological research, however, is concerning and indicates that the medication trial procedure has to be more stringent. To clarify the biochemical and molecular mechanisms underlying drug-induced hepatotoxicity, a wide range of medications have been thoroughly studied in both people and animals. A pattern of liver damage is developing, and the typical side effects of most of the drugs are visible [16]. However, some +

medications, most notably rifampicin, can cause hepatotoxic side effects, such as isolated hyperbilirubinemia, cholestasis, and liver damage. Therefore, a higher index of suspicion and familiarity with the most widely used medications, including statins, acetaminophen, diclofenac, pyrogallol, and anti-tubercular medications, should be used in the diagnostic process.

Rifampicin

Hepatitis is present in 0.46 percent of patients undergoing anti-tubercular therapy and taking anti-tubercular medications. Compared to research from wealthy nations, the hepatotoxic response was noticeably more severe in Indian individuals [17,18]. The gastrointestinal tract absorbs it well (90%), and most of it is complexed to circulating plasma proteins. It has previously been demonstrated that oxidative stress and rifampicin-induced hepatotoxicity are related in experimental rats [19]. Rifampicin damages hepatic cells by increasing the covalent binding of reactive acetyl hydrazine metabolites to hepatocyte macromolecules and by potently inducing cytochrome P450 activity. Furthermore, desacetylrifampicin, another reactive metabolite of rifampicin, is responsible for further negative effects of the drug. It has been shown to compromise membrane integrity and change membrane permeability [20,21]. Long-term exposure significantly lowers glucose-6-phosphatase activity, which may help to explain the high lipid peroxidation levels [22]. Anti-tubercular drugs raise intracellular calcium levels, which causes phospholipase A2 to be synthesized and catabolize membrane phospholipids [23]. Moreover, liver problems brought on by anti-tubercular medications that interfere with hepatic lipid deposition mechanisms have been documented to exhibit fatty liver and CYP2E1 activation[24]. The elevated uptake of LDL by circulatory tissues may possibly be the cause of the hypercholesterolemia brought on by these drugs [25].

Isoniazid

An anti-tubercular medication called isoniazid is used to kill living bacteria, either alone or in combination with other medications. Given that the bacteria may be inactive for a considerable amount of time, the isoniazid regimen usually lasts six to twelve months. Research has shown that isoniazid treatment is associated with severe and fatal hepatitis [26]. People over 65 are more likely to get hepatotoxic responses. Additionally, frequent alcohol intake may increase the danger of contracting hepatitis. In patients with the condition, the liver processes isoniazid; liver damage does not appear until three months into treatment. Mono-acetyl hydrazine (MAH), non-toxic

diacetyl hydrazine, and a number of other minor metabolites are produced when isoniazid is converted to acetyl-isoniazid by N-acetyl transferase 2 (NAT-2) [27]. It has been demonstrated that tissues suffer when reactive oxygen species (ROS) are produced by the reactive metabolites of MAH [28]. Isoniazid inhibits glutathione production, reduces catalase activity, and interferes with the action of the antioxidant glutathione peroxidase in rats [29]. Furthermore, hepatic cellular damage has been linked to acetyl-hydrazine, a non-polar metabolite of isoniazid, particularly in people with the homozygous CYP2E1 c1/c1 genotype, which increases CYP2E1 activity.

Acetaminophen

When used at therapeutic dosages, acetaminophen (APAP), an analgesic and antipyretic that functions similarly to other analgesics, is quite safe [30]. However, when administered in high dosages, the In many countries, related hepatotoxicity is generally the major cause of drug-induced liver malfunction and a major concern[31].The mechanisms of acetaminophen's hepatotoxicity have been carefully studied. Hepatotoxicity incidence varies with age, with neonates experiencing lower incidences than older children and adults. Rare events result from the low oxidative enzyme activity in neonates. The suppression of a delayed hypersensitive reaction to dinitrochlorobenzene [32] illustrates how acetaminophen-induced hepatic damage leads to a functional impairment of the immune system. Following liver damage brought on by post-APAP, corticosterone enhanced lymphocyte depletion, according to later studies conducted on rats with adrenalectomies. Acetaminophen is changed by the CYP enzymes into the Reduced glutathione (GSH) subsequently detoxifies the N-acetyl-p-benzoquinone imine to a crucial level. GSH is depleted as a result of this activity, which permits the product to bind to macromolecules covalently [33, 34]. Significant liver damage has been shown in animal models of APAP overdose. Only when acetaminophen-protein adducts are present do the hepatocytes experience necrosis. Superoxide is neutralized by nitric oxide (NO), which creates peroxynitrite., is thought to be the mechanism by which APAP toxicity spreads. This results in protein nitration (3-nitrotyrosine) and subsequent tissue damage. Increased oxygen/nitrogen stress is linked to acetaminophen toxicity [35].

Diclofenac

Hepatotoxicity from diclofenac is a prominent example of idiosyncratic liver injury; approximately 15% of patients on regular diclofenac treatment exhibit elevated hepatotoxicity markers. Diclofenac can cause liver damage in women 65 years of age and older. Although there have been reports of cholestatic Diclofenac mostly shows up as a hepatocellular pattern of liver disease, with some cases resembling autoimmune hepatitis and liver damage [36]. CYP2C8/9 and UDP-glucuronosyltransferase-2B7 metabolize diclofenac, producing unstable intermediate chemicals that covalently alter proteins and increase the risk of hepatotoxicity in patients. Additionally, helper T cells are able to identify the neoantigens produced when reactive metabolites covalently bind with self-proteins, activating them and causing an impact on effector cells. The surface expression of MHC I molecules and the presence of diclofenac adducts make hepatocytes vulnerable to liver injury caused by T cells. But when B cells recognize the diclofenac adduct on the hepatocyte plasma membrane, they become plasmacytes, produce antibodies, and eventually cause the hepatocytes to die immunologically [37].

Alternative drugs

Other commonly used drugs that harm the liver include the antiepileptic drug valproic acid, which can damage the liver in about 20% of patients; antibiotics like ciprofloxacin, erythromycin, and amoxicillin can cause jaundice, acute hepatotoxicity, and hepatolithiasis; chlorpromazine is known to cause jaundice; amiodarone has been indicated as the major cause of severe hepatotoxicity in human and animal studies as well as oral contraceptives can contribute to liver damage.

The hepatotoxicity mechanism caused by medications

is complex and multifaceted. While some medications induce liver damage only in susceptible individuals and show symptoms after days or weeks, others are immediately toxic and exhibit hepatotoxic effects in a dose-dependent manner within hours of exposure. These reactions are often idiosyncratic rather than allergic. Drug interactions can significantly increase the degree of harm, even though the medications are hepatotoxic by nature. Hepatotoxicity is largely caused by drug-induced intrahepatic cholestasis, and since the 1950s, a lot of research has been done on the connection between cholestasis and carcinogenicity. A detailed analysis of the role of reactive oxygen species (ROS) in cellular damage suggests that important, potentially fatal drug responses may be explained by the covalent interaction of ROS and reactive intermediates with various macromolecules [38]. Hepatotoxic substances have been proven in numerous studies to create free radicals and reactive metabolites [39]. The lowering of tissue GSH, an intracellular antioxidant, is directly related to lipid peroxidation of membranes. This

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leads to the functional decline of these structures, which can be fatal in cases of severe damage. Research shows that oxidative damage to erythrocytes causes changes in the erythrocyte antioxidant system, increased lipid peroxidation (LPO) of the membrane, and reduced membrane integrity, all of which lead to cell death [40].

The function of antioxidants

The effectiveness and potential of natural antioxidants in reducing drug-induced liver damage intrigues the researchers. Natural compounds are used in Chinese and Indian cultures as traditional treatments for liver diseases, which are becoming more common [41]. These are the possible sources of novel therapeutic compounds that may be applied to inhibit liver damage. In animal and laboratory cell models of liver injury, triterpenes, flavonoids, and polyphenol-rich natural products have been shown to be effective hepatoprotective agents. Natural goods are said to provide protection because of their antioxidant materials, which can stop free radicals in the cellular entity and stop reactive oxygen species from damaging membrane lipids and macromolecules. Furthermore, its interface with several CYP isoforms, capacity to increase GSH synthesis, level of Phase II/antioxidant enzyme activity, and ability to prevent toxins from entering cells enhance the protective qualities of natural products [42]. Natural compounds that include polyphenols are thought to have hepatoprotective and chemopreventive properties. Numerous studies have looked at the biochemical, genomic, and proteomic modes of action of natural products over the last ten years. The most extensively studied natural compounds with hepatoprotective properties are silymarin, resveratrol, curcumin, and ginkgo; these are credited with their notable effectiveness, low or minimal toxicity, and accessibility.

Sativa Nigella

Thymoquinone, the major ingredient of Nigella Sativa (black seed), is a naturally occurring dietary antioxidant that scavenges radicals and has antioxidant action [43]. Thymoquinone has significant antioxidant properties that allow it to scavenge reactive oxygen species and begins its antioxidant impacts at low concentrations owing to the redox possible of its quinone structure and its excellent ability to pass through the morphological barriers in subcellular compartments[44]. The delightfully spicy seeds of the naturally occurring plant Nigella sativa are used to make Mediterranean cheeses, pastries, and curries. Because Nigella Sativa seeds contain around 100 chemical components, including important fatty acids, they are utilized in both traditional and modern medicine to handle numerous forms of illnesses [45]. Numerous earlier studies have shown that the antioxidant Nigella sativa can help reduce the side effects of some drugs. While Badary et al. discovered that Nigella Sativa's strong thymoquinone properties may lessen doxorubicin-induced hyperlipidemic nephropathy, Alenzi et al. [46] showed that Nigella Sativa protected against cyclophosphamide-induced toxicity, a commonly used anticancer medication. By controlling antioxidant enzyme levels and cellular protein oxidation through its antioxidant mechanism, Nigella sativa's antioxidant qualities can lessen gentamicin-induced nephrotoxicity and increase cyclosporine A-induced cardiotoxicity. According to Mansour's research [47-49], Nigella Sativa lessens chemical toxicity, particularly that of carbon tetrachloride and mercuric chloride, as well as the hepatotoxicity of carbon tetrachloride and the renal toxicity of mercuric chloride (Nagi and Almakki) [50]. By increasing plasma testosterone levels, reducing the number of morphologically abnormal sperm, and boosting sperm motility and viability, nigella sativa seeds may mitigate the symptoms of testicular toxicity brought on by ongoing colchicine treatment. Additionally, thymoquinone from Nigella sativa is thought to be an antidote for natural poisons such lipopolysaccharides and D-galactosamine as well as mycotoxins like aflatoxin B1. By preventing the synthesis of malondialdehyde, a lipid peroxidation signature, it offers protection against aflatoxin B1-induced hepatotoxicity. This lessens the possibility of any histopathological, hematological, or biochemical alterations brought on by an aflatoxin-contaminated diet [51,52].

Curcumin

One common natural treatment for drug-induced toxicity is curcumin. Turmeric is mostly found in the roots of the plant Curcuma longa Linn. In the intestines and livers of rats and humans, it hydrolyzes into hexacurcumin, tetrahydrocurcumin, glucuronides, and sulfates [53]. It is anti-inflammatory, antiviral, anti-carcinogenic, anti-choleretic, and anti-infectious. Because it suppresses the activity of the transcription factor NF-kB, which prevents the creation of the enzyme cyclooxygenase 2, it is most likely a hepatoprotectant [54]. When used with conventional chemotherapeutic UV agents, curcumin, the most potent MDR modulator among curcuminoids, can reduce multidrug resistance (MDR) in malignant cells. Curcumin suppresses pro-inflammatory induction via activating peroxisome proliferator-activated receptor-gamma (PPAR-gamma), and it has anti-inflammatory properties, including immunosuppression and anti-rheumatic

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actions. Soliman et al. claim that curcumin restores the liver's antioxidant capacity, protecting the liver from hepatic damage caused by paracetamol. They found that although curcumin reduced the expression of antioxidant genes, it effectively counteracted the effect of paracetamol on raising the levels of matrix metalloproteinase-8 (MMP-8), interleukin-1β (IL-1β), IL-8, tumor necrosis factor-α (TNF-α), and acute phase proteins. In animal studies, curcumin provides hepatoprotection against liver damage caused by cisplatin, alcohol, and heavy metals [55].

The Ginkgo biloba.

Ginkgo biloba extract possesses antiplatelet, immunomodulatory, apoptosis-inducing, memory-boosting, and cognitive-enhancing properties. The medicinal benefits of this herbal remedy for hepatotoxicity, chronic refractory schizophrenia, neurological abnormalities, and sleep problems in depressed people have been shown in recent investigations. Organic acids, flavonoids like kaempferol, and terpenoids like ginkgolides and bilobalaides make up the majority of ginkgo. Ginkgo seems to be a promising additional treatment for diabetic patients with ischemic cardiac injury. By influencing the liver's metabolic enzymes, which in turn influence the amounts of endogenous antioxidants such glutathione (GSH) and antioxidant enzymes, ginkgo biloba extract ingestion can change hepatic metabolism. Hepatic metabolism disruption may lead to decreased clearance of concurrently administered medicines, particularly those with low renal and hepatic elimination [56].

Vitamins

The use of nutritional supplements, especially vitamins, as supplemental or protective antioxidant agents to lessen and prevent toxicity brought on by different drugs and pollutants is the subject of recent studies. The antioxidant properties of vitamins E and C, which lessen oxidative stress, lower lipid peroxidation, and improve the action of antioxidant enzymes, were found in the study[57]. Therefore, vitamin E may offer protection against cisplatin-induced nephrotoxicity, while vitamin C may lessen the toxicity of amiodarone-induced thymocytes by restoring cellular glutathione levels, as seen by Cekic et al. Furthermore, Osman et al. confirmed that vitamin C's antioxidant qualities can reduce hepatotoxicity associated with prolonged usage of monosodium glutamate. Similarly, it has been shown that vitamin C and E combinations protect against metal-induced toxicity, such as oxidative liver damage caused by cadmium, and that vitamins E and D work in concert to prevent fluoride-induced reproductive toxicity. The extensive body of published research offers strong evidence that vitamins C and E can increase the toxicity of insecticide exposure; by reducing lipid peroxidation, these vitamins can also reduce oxidative stress and harmful spermatogenesis disruptions brought on by the polycyclic chlorinated hydrocarbon insecticide endosulfan. As antioxidants, vitamins C and E can improve testicular functioning, liver, and kidneys by reducing oxidative stress brought on by exposure to macrocyclic lactone pesticides. (abamectin) [58].

Conclusion

Drug-induced hepatotoxicity has a major impact on patient health and drug safety profiles, making it a serious worldwide health concern. Hepatotoxicity has a variety of pathophysiological pathways, although oxidative stress is the main modulator of liver damage. Despite the liver's heightened vulnerability to toxicity as the primary site of drug metabolism, the utilization of antioxidants presents a means to mitigate the adverse effects of drug-induced liver impairment.

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Conflict of Interest

None to declare.

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