Drug Development and Hepatotoxicity: A Comprehensive Exploration of Medical Advancement

Laxmipriya Nayak, Prof (Dr) Ravinesh Mishra, Dr. Bhartendu Sharma

Laxmipriya, M.Pharm. Department of Pharmacology, Baddi university of Emerging Sciences & Technology, Himachal Pradesh, India
Prof (Dr) Ravinesh Mishra, School of Pharmacy and Emerging sciences, Baddi University of Emerging Sciences & Technology, Himachal Pradesh, India
Dr Bhartendu Sharma, School of Pharmacy and Emerging sciences, Baddi University of Emerging Sciences & Technology, Himachal Pradesh, India

ABSTRACT

The research and manufacturing of novel compounds for medical use is necessary for the production of new drugs. Many medications with differing effects on health have been introduced throughout history. While some have proven advantageous, others have had unfavourable or even fatal consequences. This means that the process of introducing novel medications to the market is drawn out and entails extensive testing. First, medical problems and their symptoms are identified. Next, the therapeutic effects in cells and animal models are evaluated, which can have both favourable and negative outcomes. Peptide alterations' effects on tissue and cell structures, which in turn affect patient health, must be studied in order to gain a thorough understanding of medical disorders. Because the liver is located between the bloodstream and the gut, it plays a particularly important role in drug metabolism. Hepatotoxic chemicals are processed by it, and the resultant effects include pale stools, dark urine, stomach pain, frequent vomiting of blood, and exhaustion. Hepatotoxicity research frequently employs in vitro liver preparations and animal models to investigate the potential positive and negative effects of medications. Historical accounts detail the emergence of treatments for hepatitis, ranging from homeopathic cures to contemporary medications like nucleoside analogues and interferon. The development of safe and effective drugs requires a thorough understanding of liver function and drug interactions, underscoring the importance of thorough research in drug discovery and hepatotoxicity management.

Keyword: *Drug Development, Medical Treatment, Therapeutic Effects, Peptide Modifications, Liver Metabolism, Hepatotoxicity Animal Models, In Vitro Studies, Hepatitis Outbreaks, Interferon, Nucleoside Analogues, Drug Safety, Liver Function, Adverse Drug Reactions*

1. INTRODUCTION

The development and production of innovative substances that help in the medical management of health conditions is essential for the creation of new medications. There have been plenty of drugs released in history, a few of them possess beneficial effects on health, whereas some may have adverse, life-threatening, or just slight consequences on the functioning of the body. Consequently, the entry of these novel medicines into the marketplace demands a long time [1,2]. For an experimental medicine to qualify as appropriate for consumption, it has to pass via an extensive number of trials. Starting with the identification of the medical condition plus its manifestations that reduce the standard of life, novel remedies have been found. The toughest component when developing an innovative drug involves assessing its therapeutic effects in cells and experimental animals, that might result in positive as well as negative consequences. Therefore, these detrimental consequences can be thoroughly examined employing many different kinds of model animals. The most important step of figuring out the root cause of a medical condition is to understand how peptides undergo modifications, how this affects the structure of tissues and cells, and the way these

modifications influence well-being of patients [3,4]. The discovery of drugs isn't limited to recording beneficial outcomes; it is equally necessary to keep track of adverse reactions so as to avoid these research studies from having an impact on animals. Species such as rodents, guinea and additional species are utilized to conduct these experiments. It usually takes an extended period and a lot of effort to create drugs that are novel. Many medicinal products were eliminated throughout the last half-century, whereas hundreds of novel pharmaceuticals are currently on the market [1,2]. In the current time period, contaminants, chemicals, and industrial debris containing toxic substances are mixed together in the environment in which we live, especially the atmosphere and freshwater which is primarily needed by the bodies of humans to work efficiently. The organ known as the liver residing in animals. The liver is an organ that performs an integral part in the breakdown of medication thanks to its physical position that exists between the gut and the bloodstream [4,5]. The human liver is a versatile organ that manages both secretion and detoxifying tasks. It has a weight of approximately 1.5 kilograms in an adult male, which makes it one of the biggest glands in the human physique [6]. Once a drug develops a therapeutic response, it requires biological transformation in the cells of the liver. From intestinal absorption and portal venous circulation, an immense quantity of vitamins and minerals and foreign chemicals travel into the hepatocytes. Hepatotoxic substances such as kava, ephedra, and galactosamine are additionally metabolized by the liver's cells to hazardous byproducts [3].

The medical condition termed hepatotoxicity, which is additionally referred to as cirrhosis of the liver, is a condition that occurs when the functioning of the liver gets damaged by a wide range of conditions. These circumstances comprise foreign substances, encompassing pollutants from the environment, chemicals, drugs, dosages for therapeutic purposes, and chemical substances activity that has come into touch with the internal organs of a person. The liver purifies the human body against many different kinds of harmful substances that arise by means of chemical responses or when consuming any harmful substance. Like everyone will understand, the body of a person is capable of recognizing any strange occurrence, irrespective of how insignificant, severe, or dangerous it might seem. Symptoms of such disorders includes black urine, pale feces, cramping in the abdomen, blood vomit frequently, and fatigue. The smooth endoplasmic reticulum, formerly referred to as the metabolism clearance residence, exists in the liver's cells and serves as a catalyst for each intrinsic and exterior drug breakdown.

Omega-3 fatty acids, lipids, and steroids are converted to energy by endogenous procedures however prescription drugs gave for medicinal reasons or illegal drugs are broken down by external mechanisms. The mitochondria, a cellular organelle that generates ATP to support or accelerate the metabolic processes response, suffers damage through these chemical events. Abnormal levels of oxidizing agents are produced as a consequence of injury to mitochondria, that may cause damage to liver cells and specific metabolic enzymes like CYP2E1 which belongs to the cytochrome P-450 family. Bile duct cell lines might go through apoptosis primarily as a consequence to mitochondrial damage, that may cause additional damage the functioning of the liver. It may be possible for chemicals to negatively impact organs at the molecular or cellular level via complex interactions which take place at cellular levels & rely on either direct or indirect interactions with liver cells, that involve RNA, protein, and DNA [8].Hepatic toxicity is researched utilizing a wide range of animal models- in vivo approach is not often employed, whereas the in vitro hepatic preparations has been used more often because it offers different viewpoints at every phase of investigate toxicity.

2. BACKGROUND

In 1957, interferon became known for the treatment of hepatotoxicity. Following that, many drugs and immunizations have also been developed for the same reason. Following then, PMEA anti-HBV activity was discovered in 1990. Hepatitis B and HIV treatment alongside 3TC anti-HBV and anti-HIV activity was first detected in 1991. Hepatitis B therapy using Interferon-Alfa 2B gained authorization in 1991.Entecavir's anti-HBV activity for hepatitis has been identified in 1998. Lamivudine (3TC), the very first nucleoside analogue of HBV, received FDA approval (1). Hepatitis was once an immense mystery, yet the enigma is about to be revealed. The first therapeutic text goes to the age of Sumerian’s clay tablets, who mention jaundice in the 3rd millennium B.C. Devil Ahhazu (2) is the hepatitis-causing agent. Hippocrates disclosed the clinical manifestations of jaundice, which result in mortality in less than 12 days, from the years 375 and 460 B.C. Meal with water and honey was utilized as a remedy for this clinical symptom (3). First, there are several proofs of hepatitis which were propagated through Greeks and Romans but were erroneously identified for leptospirosis and malaria. Pope Zachary advised that the most effective remedy regarding this matter is isolation. During battles in the middle of the nineteenth century, especially the capture of Saint-Jean-d’Arcy in 1799 and the American Civil War (1861–1865), many cases of hepatitis circulated all over military groups. Hepatitis has been estimated had inflicted 16 million casualties during the course of World War II, including the US Army claiming 1,50,000 cases of the infection. Several epidemics were recorded during conflicts

in the 18th century, especially the Siege of Saint-Jean-Dacre in 1799 and the Siege of Paris in 1870. An additional problem during the American Civil War (1861–1865) was the 52 000 hepatitis cases. Hepatitis contributed a total of 16 million fatalities throughout World War 2. In comparison against the German military's 4 million "the census data," the US Army reported 150 000 cases (3). Those with immunizations against smallpox are also showing hepatitis symptoms. The writer and researcher of this study is Luhrman. A number of cases are additionally linked to the consumption of gold salt or bismuth iv and orally, accordingly. There were multiple cases from the US Navy in 1942, leading to 56000 patients getting the infection upon getting yellow fever vaccine contaminated with human plasma (4). Macallum knew the difference between the two kinds of hepatitis in 1947: epidemic hepatitis, that has a short time frame for incubation, and serum hepatitis, that requires an extended incubation period (100 days of fever) (5).

2.1 Hepatitis B virus became known via a big bang

While studying lipoprotein polymorphism at the prestigious National Institutes of Health (NIH) in 1963, Baruch Blumberg and his associates noticed a surprising relationship between Australian Aborigine oxygen-rich blood and poly-transfused hemophilic serum. Though the red staining of its reaction was different, he noticed that he had come across an unknown lipoprotein (6). Australian Antigen (Au), an innovative antigen, is responsible for the observed red staining. By irony, a lab technician acquired jaundice in 1967, and subsequent study reveals the presence of Au Antigen is linked to hepatitis (7). The serum antigen associated with serum Hepatic antigen (SH antigen) was identified for the first time in 1968 under a scientist by the name of Alfred Prince employing electrophoretic technique (8). The antigens that are responsible for Au and SH later turned out to be equivalent. The relationship that exists between post-trans fusional hepatitis and blood donors was proven in a study that took place in Japan in 1972.The previously determined antigen has been renamed as the HBs antigen, and its identification is consequently necessary. Fortunately, since the beginning of the twentieth century, nearly every one of notable organizations have gone through testing for blood centers. Blumberg developed the first generation HBs antigen plasma-based vaccination. Following all of this, he filed for a patent to safeguard his own developed version of the vaccination concept, and for the first time in history, a vaccine wasn't manufactured employing tissue culture. Later, in 1976, Blumberg bagged the Noble Price in Medicine for his groundbreaking research in manufacturing the HBV vaccination and characterizing HBV (9).

2.2 Discovery of Hepatitis virus A (HAV)-

NIH scientist Stephen Finestone established the immune-electron microscopy technique in the very early months of 1977 while partnering with Kalpakian to determine an agent in the stool containing the HAV antigen while looking for the rotavirus. The HAV antigen as well as its antibodies, IgG & IgM, produce themselves in the serum, as determined by serological investigations. A vaccine emerged quickly following tissue culture experiment (10).

2.3 Discovery of hepatitis delta virus (HDV)-

Employing immunostaining, a medical practitioner titled Mario Rizzuto identified a novel antigen in 1977 while attempting to identify HBV antigen in an Italian patient. This antigen is HDV. Although it is unlike HBE and HBC antigens, this antigen has been named as delta. The medical sign of the infectious disease comes due to the delta antigen, which is transported by HBV (11).A new flawed RNA virus which requires the HBV helper antigen for replication came to light in a study performed at the NIH because of scientists John Gerin and Robert Purcell who collaborated on transmission studies on chimpanzees. The HDV RNA virus was successfully identified; it is the tiniest vector to date (12). In certain regions of the Amazon Forests as well as central Africa, this disease-causing HDV viral spreads as an endemic infection (13). Interferon Alpha, a substance that inhibits the is prenylation stage needed to prevent HDV replication, is the antiviral therapy employed for the viral infection. The most effective method of therapy to date is the HBV vaccination.

2.4 Identification of Hepatitis C Virus (HCV)-

Post-trans fusional hepatitis showed up in a study carried out at the NIH by Finestone, Purcell, and Prince in a laboratory in New York. It has been triggered by a yet-unidentified agent, and researchers are optimistic that one day they will come across this new pathogen (14,15). Experts have been trying to inject this infectious virus using post-trans fusional hepatitis victims into Chimpanzee mammals. Infectious hepatitis is highlighted by extremely contagious Antihemophilic factors VII and IX. This post-trans fusional hepatitis virus features an endoplasmic

reticulum tubule form and an additional lipid bilayer (16). This enclosed virus HCV has a molecular circumference of 45-60 nm. For many years, experts have been trying to figure out its culture and microbiological description. Then, at the CDC, Danial Bradley and Michael Houghton's analytical teams cooperated to discover the deadly Hepatitis C Virus (HCV). This finding assists in the detection of novel neglected viruses that include hepatitis G virus and blood products-transmitted virus (17).

3. Epidemiology of hepatotoxicity

Recently published information proved that the frequency of drug-induced liver injury (DILI) fluctuated between 1 per 10,000 to 1 per 100,000 (18-29). Many current studies indicate an increased incidence of toxicity to the liver. A number of Western (30-33) and Asian (34) nations generated helpful data on hepatotoxicity diagnostics and medical treatment. According to epidemiological research, Iceland shows a yearly rate of 19.1 incidents for every 100,000 inhabitants (33), while France shows a yearly rate of 13.9 incidents for every 100,000 people, including 12% of them admitted and an overall mortality rate of 6% (31). Majority liver harm-causing drugs are antibiotics, including 46% of incidents of DILI documented by the USA DILI web (35). In accordance to an Italian case-control investigation that was backed by Swedish, English, and population-based research, the prevalence of drug-induced liver injury (DILI) were 4.1 peoples for every 100,000 peoples, and 50% of the individuals harmed consumed NSAIDS (31–33). With respect to the patient category (inpatients or outpatients) & the selection time frame, ranging from 2 to 10 years (36), outcomes from multiple research methods fluctuate considerably.

The overwhelming majority of studies claim that throughout India, 58% of DILI and liver damage instances involved anti-tubercular pharmaceuticals and 11% of cases featured anti-epileptic drugs. The fatality rate associated of anti-tubercular pharmaceuticals is double that among alternative existing pharmaceuticals (37), despite this percentage fluctuates with nations (38), considering every nation offers independent ways of recommending the medication, and certain people will make use of it whereas others will not. Based on one research project carried out by clinicians in the British Isles (U.K.) from 1994 and 1999, the overall rate of injury to the liver among people consuming isoniazid is 100 for every 100,000 instances, whereas for amoxicillin-clavulanic acid was 10 for every 100,000 instances (39). The most vulnerable age categories are older people and kids, compared to young people and adults, considering their resistance to infection, suitability, and adherence to pharmaceuticals are somewhat minimal (40,41). Pregnant women are considerably more vulnerable to liver damage than men simply because of anatomy-related parameters. Higher-income individuals tend to be more likely to suffer liver failure than mid-class or poor people because consumption of additional prescription drugs such as antibiotics, steroidal products, and supplements (42).

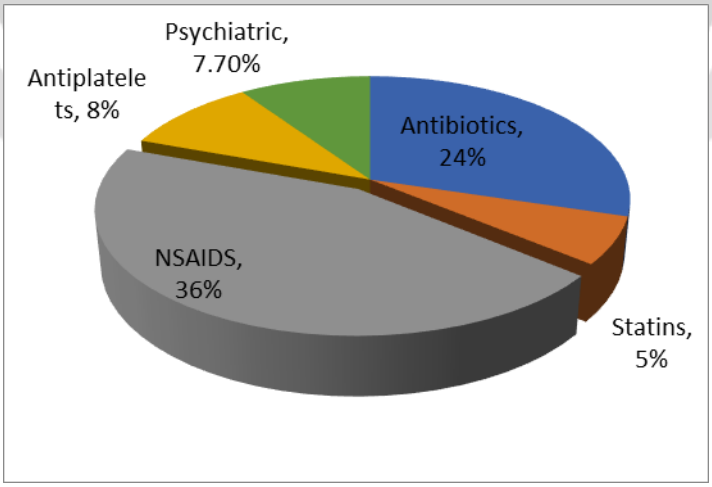


Fig -1 Percentage of instances involving drug-induced hepatotoxicity.

3.1 Cases of Hepatotoxicity based on the age-

The primary contributor to liver damage is the repeated use of pharmaceuticals like Amoxicillin-Clavulanate (46), halothane (47), isoniazid (48), and nitrofurantoin (49). Adolescent or adults may have hepatocellular liver toxicity,

however senior individuals are far more likely to suffer from cholestatic hepatotoxicity (50,51,52,53). Age isn't a big factor for certain medications (53). Hepatic toxicity with the antibiotic amoxicillin clavulanate is generally impacts adult and rarely impacts young people (55,56). Research (57, 56) indicate that taking antiepileptic medicines frequently among children promotes a rise in liver damage events.

3.2 Cases of Hepatotoxicity among Hospitalized Patients-

Only 17 out of 96 hospitalized patients (particularly older patients) who participated in Icelandic research display symptoms of liver damage, that can be brought upon through the consumption of multiple prescription drugs during the patient is at the medical center (57). Hepatic toxicity is extremely uncommon in as outpatients. Among approximately 1950 patients hospitalized to UK hospitals with an incidence rate of only 0.7%, there are just 13 individuals who display this liver damage manifestation (58). The prevalence rate of liver toxicity was 1.4% (59).

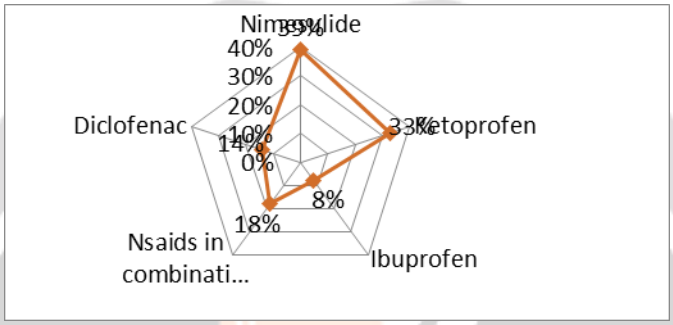
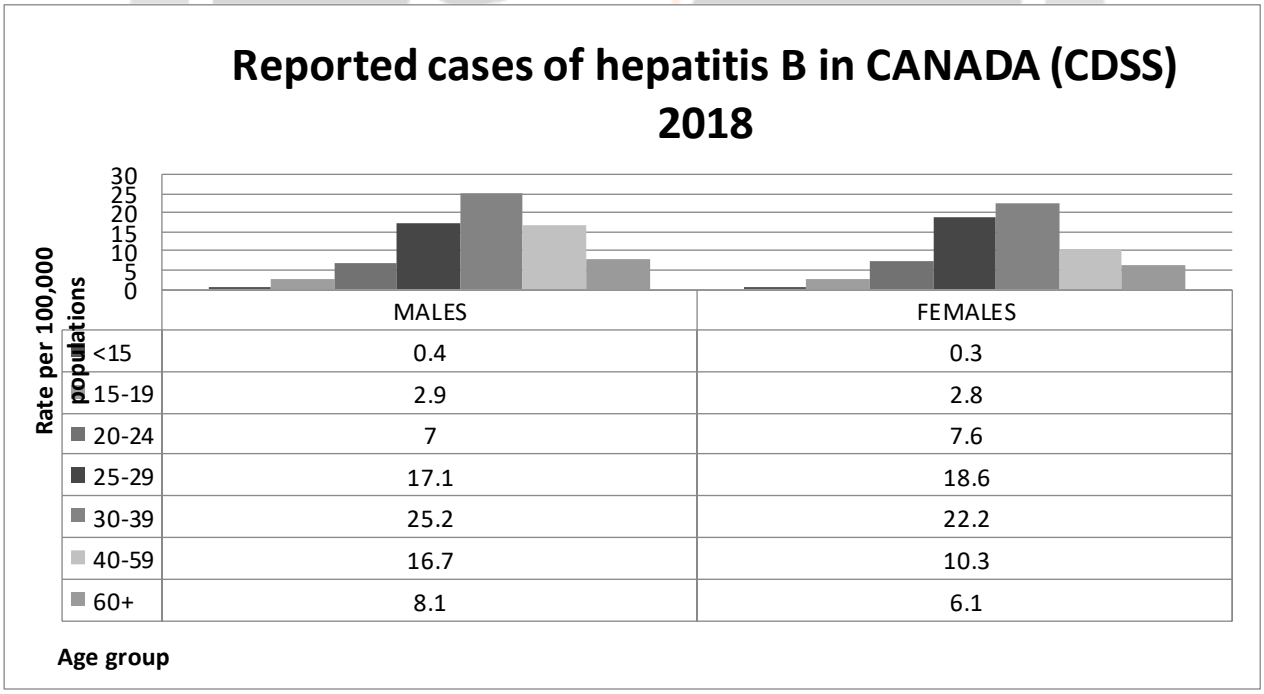


Fig- 2 (RADAR) - This radar displays the 36% of instances in the cohort study analysis of the population that were caused by NSAIDS medicines.



	MALES	FEMALES
<15	0.4	0.3
15-19	2.9	2.8
20-24	7	7.6
25-29	17.1	18.6
30-39	25.2	22.2
40-59	16.7	10.3
60+	8.1	6.1

Fig- 3 Rates of reported cases of chronic HBV infection by sex and age group in Canada, CNDSS, 2018 - Text description

4. Mechanism of action

Carbon tetra chloride (CCl_4)

CCl4 is life-threatening dependent on the quantity and duration of contact. Consequences that include Ca+ shortage, peroxidation of lipids, release of cytokines, and programmed cellular death (Apoptosis) may take place at low concentrations. Cancer, fibrosis, and encephalopathy have been created when exposed to elevated quantities [1]. During the biological transformation of CCl4 via cytochrome P450, trichloromethyl radical is generated [2].After linking up with the unsaturated fatty acids found in the cell membrane, trichloromethyl radicals, considered harmful by its very nature, promote lipid peroxidation via the cross-linking of unsaturated fatty acids [3]

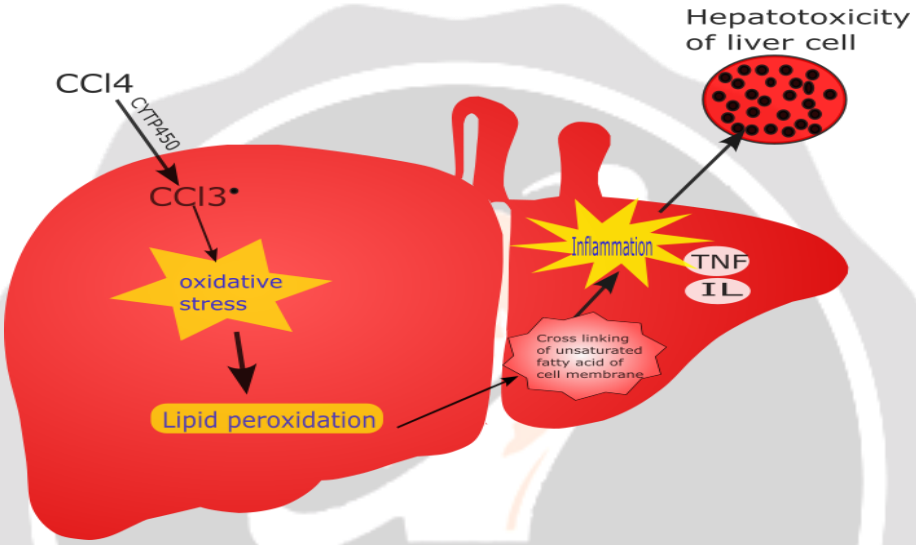


Fig -4 Mechanism of carbon tetra chloride

Isoniazid

For the medical management of tuberculosis, an isoniazid is employed. Although it displays more effectiveness & less catastrophic complications, the drug is sometimes considered to be a primary medicine. N-acetyltransferase (NAT2) is an enzyme likely helps in the breakdown of isoniazid. It converts the isoniazid directly into acetyl isoniazid, which is where acetyl hydrazine is generated via hydrolysis [4]. Acetyl hydrazine along with other intermediates efficiently adhere to big complexes like as proteins, lipids, DNA, and carbs [5], leading to cirrhosis and liver damage.

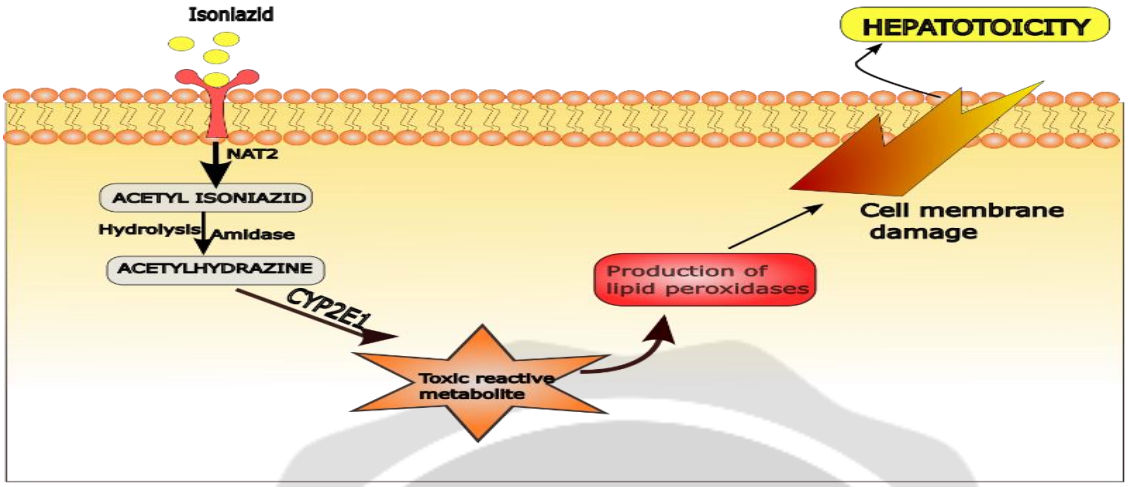


Fig-5 Mechanism of Isoniazid

Ethanol

Acetaldehyde gets created soon after the biological transformation of ethanol in with the help of (ADH) alcohol dehydrogenase [7]. Usually quite a bit quantity of ethanol is broken down through the pathways of ADH, MEOS, or the microbiota of the gut. However, when it comes a case of alcoholic's damage to the liver, this alcohol dehydrogenase enzyme functions immediately. This refers to a condition during which ADH accelerates the biological transformation from ethanol towards acetaldehyde. If the disorder becomes more severe, mitochondrial failure will take place [8].

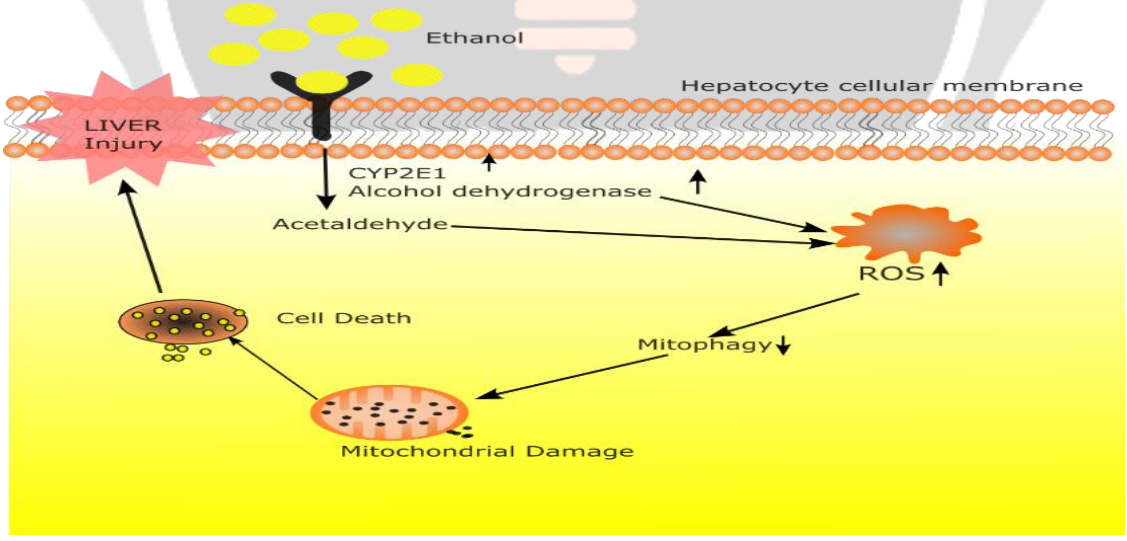


Fig-6 Mechanism of Ethanol

Methimazole

It belongs into the thioamides class and is employed for the management of hypothyroidism disorder [9]. the CYP2A6 enzyme, that processes down methimazole. It transforms methimazole to N-methylthiourea, which leads to cholestatic hepatitis [10, 11].

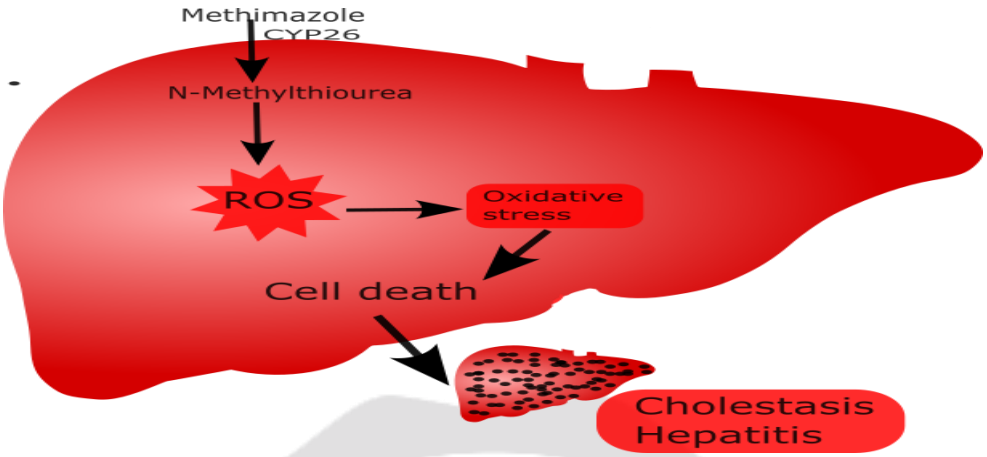


Fig-7 Mechanism of Methimazole

5. Hepatotoxicity Models

Carbon tetra chloride hepatotoxicity model

Rats from the Sprague Dawley/Albino strain were weighed (105–200g) [12] and separated into five groups. For group 1 rats, ordinary saline was used. When 75,90,105,120mg/kg of ccl4 were administered intramuscularly to group 2,3,4,5, lipid peroxidation and hepatotoxicity were witnessed. After 48, 72, 144 hours, one rat was removed from each group and sacrificed through their beheading [13].

Alcohol induced hepatotoxicity

Two groups of six rats each, Group A and Group B, were created from a total of twelve rats. Male albino rats weighing 150-200 g were weighed. Group B received treatment while Group A served as the control. For eight weeks, Group B (the treatment group) received 0.6ml/100gm/day of ethanol whereas Group A (the control group) received normal saline. Alcohol triggered hepatotoxicity in albino rats after 8 weeks (a rise in enzyme levels, mass rise in the liver, dysfunction of the mitochondria, fatty liver, etc.).[14]

Methimazole induced hepatotoxicity

Two groups (Group A and Group B) of 12 albino rats were formed based on weight. Group A rats received saline as the control group, and group B rats received 21 days of therapy with 60 mg/day of methimazole. After 21 days, the animals were sedated and slaughtered. Produced liver toxicity [15]

6. CONCLUSIONS

The development of new medications involves a detailed process of research and testing to ensure safety and efficacy. Historical data reveals that while some drugs have significantly advanced healthcare, others have posed risks, emphasizing the need for thorough evaluation. Understanding liver function and hepatotoxicity is crucial due to the liver's role in drug metabolism. Effective drug discovery relies on integrating findings from in vitro studies and animal models to identify potential risks. Ongoing research is essential to advance therapeutic options and enhance patient safety. Continued efforts in this field are vital for addressing challenges and improving drug safety.

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