IJBPAS, June, 2023, 12(6): 2412-2439

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

HEPATOPROTECTIVE ACTIVITY OF VARIOUS HERBAL PLANTS – A COMPREHENSIVE REVIEW

CHATRAGADDA RS*[1], KETHIREDDI SL[2], THALLA S[3] AND NADENDLA RR[4]

Department of Pharmacology, Chalapathi Institute of Pharmaceutical Sciences (Autonomous) Guntur-522034, Andhra Pradesh, India

***Corresponding Author: Chatragadda Ramya Sri: E Mail: ramyasrichatragadda@gmail.com**

Received 10th June 2022; Revised 15th July 2022; Accepted 3rd Aug. 2022; Available online 1st June 2023

https://doi.org/10.31032/IJBPAS/2023/12.6.6926

ABSTRACT

Liver illnesses are a serious public health concern around the world, necessitating the development of novel chemicals to combat or prevent them. As a result, researchers have been looking for natural and/or synthetic substances that exhibit hepatoprotective properties. The identification of pharmacological effects in cellular and animal models leads to the demonstration of efficacy and safety in people, which is the ultimate step in the development of new medications. In this literature, there are a variety of models for evaluating hepatoprotective efficacy in vitro, ex vivo, and in vivo. The goal of this review is to show the most commonly used hepatotoxic agents (CCl4, acetaminophen, ethanol, d-galactosamine, t-BuOOH, rifampcin and isoniazid ,thioacetamide) and biochemical parameters for assessing liver damage in the various models and there were also some plant extracts used.

Keywords Liver illnesses, novel chemicals, hepatoprotective properties, pharmacological effects, biochemical parameters

INTRODUCTION

The liver, the largest gland in the human body that serves as a storage, producing, and biotransformation organ, is located on the right side of the upper abdominal cavity and is a vulnerable target for injury. Hepatocytes are the cells that make up the liver. Proteins are synthesised in the liver, which also stores glycogen, vitamins, and iron and metabolises harmful substances and medications. Chronic alcohol intake, as

well as exposure to hazardous chemicals and medications such as paracetamol, tetracycline, antitubercular therapies, chemotherapeutic agents, and NSAIDS, cause long-term damage to the liver cells (hepatocytes). Drug-induced liver injury is a serious health concern with a wide range of symptoms, from asymptomatic elevations in liver enzymes to fulminant liver failure. Although modern medicine has supplied us with various medications to treat liver disorders, herbal medicine is chosen since it is more cost effective and is regarded to be a safe and effective treatment option with few side effects. The high cellular concentration of cytochrome P450 is linked to the liver's ability to carry out many oxidative metabolisms. Because the liver is the major organ of metabolism, it is a particularly sensitive target for pharmacological and chemical injury, with symptoms ranging from asymptomatic increase of liver enzymes to fulminant hepatic failure.

LITERATURE

Amirhossein Babaei *et al*., (2022) evaluated the Comparison of efficacy of oral fenugreek seeds hydroalcoholic extract versus placebo in non-alcoholic fatty liver disease; a randomized, triple-blind controlled pilot clinical trial. The purpose of this study is to examine if a hydroalcoholic extract of Fenugreek seeds can help adults with non-alcoholic fatty liver disease (NAFLD).using blocked randomization method, placebo-controlled, parallel trial was conducted. Treatment allocation was hidden from the investigators, participants, and statistician. There were no statistically significant differences comparing the two groups in anthropometrics, laboratory, or Fibro Scan data. The evidence for the efficacy of Fenugreek seeds extract in relation to the treatment of NAFLD was insufficient; more research is needed to examine the possible efficacy of Fenugreek in the treatment of NAFLD **[1]**. Khalid Mohammed Naji *et al*., (2021) studied the Hepatoprotective activity of melittin on isoniazid- and rifampicin-induced liver injuries in male albino rats . To see if melittin, a key polypeptide found in honeybee venom, could help male albino rats with Rifampicin and isoniazid (INH) (RIF) -induced hepatotoxicity. When melittin was given, diagnostic indicators changed; haematological changes were much higher in Melittin groups compared to the hazardous group. Low levels of DB, ALP, TB, LDH, and TSP were found in the NR group. Evidence suggests that melittin is effective in preventing acute hepatic failure caused by antitubercular drug-induced hepatoxicity and could be employed as a therapeutic agent **[2]**.

Karri Sowjanya *et al*., (2021) aimed to study the Efficacy of *Phyllanthus niruri* on

improving liver functions in patients with alcoholic hepatitis: A double-blind randomized controlled trial. An herbal remedy that has been used for centuries. In preclinical and clinical studies, *Phyllanthus niruri* has been found to be hepatoprotective. There have been no clinical trials to date that have evaluated its efficacy in the therapy of alcoholic hepatitis. Determine whether P. niruri has made a significant difference. The serum did not reveal any liver or renal function indicators. Overall antioxidant levels, as well as hunger stimulating activity, increased dramatically with P. niruri. dosing to mild–moderate alcoholic hepatitis patients, P. niruri exhibited improvement in total antioxidant levels with appetite stimulating activity when compared to a placebo **[3]**. Mervat Mohamed *et al*., (2021) evaluated the Modulation of Liver P-Glycoprotein Expression May Contribute to Gossypin Protection against Methotrexate-Induced Hepatotoxicity Methotrexate (MTX) is a broadly used anticancer. The purpose of investigation was to see if gossypin could protect the liver against MTX toxicity. The levels of liver enzymes and oxidative stress indicators were measured. Gossypin is a flavonoid that has a hepatoprotective and anticancer action as a primary side effect. Hepatic caspase 3 and nuclear factor kappaB (NFB) were studied histopathologically as well as immunohistochemically. Gossypin may be a useful adjuvant therapy for MTX toxicity, as it protects the liver through antioxidant, anti-inflammatory, and antiapoptotic pathways. MTX caused a considerable increase in liver enzymes and hepatic architectural distortion as well as a rise in in hepatic collagen. Gossypin pre-treatment improved the previous parameters, restored the normal hepatic architecture, reduced the hepatic fibrosis, and regained nearly normal expressions for BAX, TGF-β, caspase 3, and NFκ-B. Gossypin caused more reduction in P-gp hepatic expression upon assessment **[4]**.

Maria Valentina Ignat *et al*., (2021) Aimed to study the plants of the Spontaneous Flora with Beneficial Action in the Management of Diabetes, Hepatic Disorders, and cardiovascular disease. The current pharmacological study is testing in the management of safety and efficacy of and liver disorders, diabetes, and cardiovascular disease. Natural medicinal plant items are examples of alternative therapeutic aids. More consideration could be given to the use of natural products. Dandelion leaf and root extracts, for example, can help to prevent liver cancer, reduce insulin resistance, and lower overall triglyceride and cholesterol levels. mulberry leaves extracts indicated that they could decrease palmitic acid-induced

lipotoxicity, improve superoxide dismutase expression, increase total cholesterol and bile acid excretion and improve insulin resistance on recent studies. Chicory root extracts are high in chicoric acid, chlorogenic acid, and polysaccharides, which help to promote satiety, reverse insulin resistance, and improve lipid metabolism. The anti-inflammatory, hepatoprotective, antioxidant, hypolipidemic, and hypoglycaemic effects of Morus nigra L., Taraxacum officinale L., and Cichorium intybus L. have been demonstrated to be effective in administration of obesity, Type 2 diabetes, and non-alcoholic fatty liver disease, dyslipidaemia **[5]**. Hasya Nazli GOK *et al*., (2021) performed a preclinical study on the Hepatoprotective Effect of Pollen Extract of *Pinus brutia Ten*.(Red Pine) in mice and Phenolic Acid Analysis . In the present study , pollen ethanol extract . Upon P.brutia investigation the possible hepatoprotective activity using a mouse model of CCL_4-induced hepatotoxicity. Because pollens are known to be high in phenolic acids, the extracts were analysed using high performance column chromatography (HPLC).Among the phenolic acids analysed Vanillic acid is the main component in pollen extract and other phenolic acids were detected that are responsible for its hepatoprotective properties. The findings led researchers to believe that pollen extract from red pines could be a viable hepatoprotective agent. Vanillic acid, as well as other phenolic acids found in the pollen extract, appears to be responsible for the pollen extract's extraordinary hepatoprotective activity **[6]**.

Paudel Kiran *et al*., (2021) investigated the hepatoprotective effect of *Berberis aristata DC*. *Berberis Aristata* DC belongs to the family Berberidaceae, Native to the Northern Himalaya region, Nepal, India, and Pakistan, this shrub is employed in alternative medical systems. "Daruharidra and Chitra" is the most common name for it. It's commonly used as a hepatoprotive, tonic, in urinary disorders, skin illnesses, diaphoretics, diuretics, and the treatment of diarrhoea, jaundice, and syphilis. Berberine is a Daruharidra natural substance that lowers hepatocyte inflammation in the liver. On the basis of modern scientific findings and Classical Ayurvedic references, the study looked into its hepatoprotective properties. Berberis aristata DC has been tested by the researchers for its various effects of the body. In Ayurveda, it is been used in many diseases as a combined ingredient and single drug of medicine. Daruharidra has been utilised as a medication since the Vedic, Upanishad, and Samhita periods. Experimental and clinical investigations suggest that it has hepatoprotective qualities against numerous liver-related

disorders, is antioxidative, and has properties in Ayurveda such as Netraroghara, Mukharognasaka, Yakritvikarnasaka, and Plihavikarhara **[7]**. Qiang Su, *et al*., (2021) Aimed to study the Antituberculosis Drugs (Rifampicin and Isoniazid) Induce Liver Injury by Regulating NLRP3 Inflammasomes . Anti-TB drugs frequently cause liver injury in patients undergoing pulmonary rehabilitation. tuberculosis, and the mechanisms of these injuries must be investigated. The histopathological changes were occurred in liver tissue are examined by H&E staining. Additionally, the levels IL-33, IL- 1β, IL-18, ASC , NLRP3, and cleaved-caspase 1The expression of these genes in liver tissues was also studied. The expression of CYP2E1 and NAT2 was determined using QRT-PCR. The effects of NLRP3-targeted siRNA were investigated in vitro. The objective of this study is to was to see if the NLRP3 inflammasome was implicated in antituberculosis drug-induced liver damage (ATLIs). Upon findings INH and RIF has the ability to kill normal liver tissue, trigger an inflammatory response, and control OS. drug-metabolizing enzymes and the antioxidant defence system by accelerating the activation of NLRP3 inflammasomes. Hereby, NLRP3 inflammasomes might be the key factors involved in INH- and RIF-induced liver injuries **[8]**.

Irina Ielciu *et al*., (2021) studied the Hepatoprotective Activity and Oxidative Stress Reduction of *Rosmarinus officinalis* L. Shoots Tincture in Rats with Hepatotoxicity Induced by Experiment *Rosmarinus officinalis* L. The aim of the research is to create a fresh viewpoint on a therapeutic product derived from this species and to examine its hepatoprotective properties. Polyphenols and terpenoids are the tested substances, which are recognised and quantified with the help of HPLC–UV–MS and GC–MS. The DPPH, FRAP, and SO tests were carried out. to investigate antioxidant activity in vitro. significant antioxidant capacity was proved in tested tincture of in vitro studies . Therefore, due to its chemical composition, the studied vegetal product belonging to pharmaceutical formulations , rosemary could be an important raw material, contributing to the improvement of human health through its hepatoprotective properties and antioxidants, having substantial anti-free radical actions, which could be effective in preventing liver tissue damage **[9]**. Dan Cao *et al*., (2021) Aimed to study the Combined Metabolomics and Network Toxicology to Explore the Molecular Mechanism of *Phytolacca acinosa* Roxb -Induced Hepatotoxicity in Zebrafish Larvae in Vivo. For a long time, *Phytolacca acinosa Roxb (PAR)* has been widely used as a diuretic medication to

treat edoema, swelling, and blisters. There are still unclear on the toxic effect mechanism . To investigate PAR-induced hepatotoxicity in zebrafish larvae, researchers used a metabolomic method using network toxicology. liver injury was caused by PAR, and apoptosis in zebrafish, abnormal liver function. PAR-treated endogenous metabolites had considerably higher levels of arachidonic acid, resulting in in vivo oxidative stress. The exposure of PAR As a result of the abnormal liver function and disturbance in amino acid metabolism, hepatocyte apoptosis is induced, resulting in liver injury **[10]**.

Hartmut Jaeschke *et al*., (2021) Evaluated the Recommendations for the use of the acetaminophen hepatotoxicity model for mechanistic studies and how to avoid common pitfalls. Acetaminophen (APAP) is an antipyretic and analgesic drug that is safe in therapeutic levels but can induce serious liver damage and even liver failure if used in excess. The therapeutically relevant results of this model are primarily utilised to investigate the drug-induced liver damage, as well as to assess prospective treatment approaches. However, the model's complexity necessitates pathophysiology expertise in order to generate reliable results and mechanistic insights that can be applied in the clinic. Many studies using this model are flawed, NRF2, nuclear factor erythroid 2-related factor 2 is a nuclear factor that is related to erythroid 2.; PUFAs, polyunsaturated fatty acids; ROS, reactive oxygen species; SMAC/DIABLO, low-pI second mitochondria-derived caspase activator/direct inhibitor of apoptosis-binding protein; TLR, toll like receptor; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labelling; UGT, UDP-glucuronosyltransferases **[11]**.

Satyanarayana R Pondugula *et al*., (2021) evaluated A clinically relevant combination treatment with doxorubicin and cyclophosphamide does not induce hepatotoxicity in C57BL/6J mice. Chemotherapeutic exposure over time can have serious side effects, including hepatotoxicity. Several malignancies, including leukaemia, lymphoma, and breast cancer, are treated with doxorubicin (DOX) and cyclophosphamide as a chemotherapeutic combination (CPS). Hepatotoxicity can occur when DOX and CPS are used together. To see if giving DOX and CPS together at the doses that are clinically relevant and frequencies causes hepatotoxicity. Alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin, albumin, globulin, and total protein levels were not affected by CPS or DOX treatment. Similarly, there was no discernible change in liver histology when DOX and CPS were given together. The use of DOX and CPS, on the other hand,

led in an increase in aspartate aminotransferase levels in the blood (AST). Increased serum AST levels were likewise linked to higher serum creatinine kinase (CK) levels, implying that the increased serum AST levels are most likely related to muscle injury caused by the co-administration of CPS and DOX. Our findings demonstrate that co-administration of CPS and DOX at dosages that are therapeutically relevant and frequencies did not cause severe hepatotoxicity in mice for the first time **[12]**.

Yukun Wang *et al*., (2021) Aimed to study the Drug-induced liver injury (DILI) is the major cause of clinical trial failure and post marketing withdrawals of approved drugs. Using a big collection of 2608 compounds as a starting point, an in-silico model based on the approach of collaborative decision-making was created for DILI assessment in this study. The hybrid quantum particle swarm optimization (HQPSO) algorithm was used to optimise the parameters and features of each sub model. The frequency-weighted and distance (FWD)-based technique was used to determine the application domain. With accuracy, sensitivity, and specificity, the proposed model correctly The substances in the test were expected set. The substructures are regarded as structural alerts in hepatotoxicity evaluation. The method has benefits in the form of data size, transparency, and uniformity of the modelling process, as well as accuracy and trust of forecast findings. The tool for virtual screening in the early stage of drug development **[13]**. Tim Brecklinghau *et al*., (2021) studied the hepatocyte export carrier inhibition assay improves the separation of hepatotoxic from non-hepatotoxic compounds . The risk of human drug-induced liver harm is assessed using in vitro and silico approaches. The method relies on data from a cytotoxicity test in cultured human hepatocytes and information about a test chemical's maximal blood concentration (Cmax) at a certain dose, which can be predicted using physiologically-based pharmacokinetic modelling. In this work, we compared a test that assesses bile acid export carrier inhibition, such as MRP2 or BSEP, to an existing approach to see if it enhances the distinction between hepatotoxic and non-hepatotoxic drugs. The 5-chloromethylfluorescein diacetate (CMFDA) export assay As a result of this, was founded. For some recognised BSEP and/or MRP2 inhibitors, the CMFDA assay yielded significantly lower EC10 values than the CTB cytotoxicity test. We find that combining the CMFDA assay with an in vitro test battery changes the distribution of hepatotoxic and non-hepatotoxic substances in a group of drugs that includes bile acid export carrier inhibitors **[14]**.

DA Sindhughosa *et al*., (2021) Aimed to study the Evaluation of Mortality Risk in Liver Cirrhosis with Albumin- Bilirubin (ALBi), Platelet-Albumin-Bilirubin (PALBi), and Fibrosis-4 (FiB-4) Scores. The (MELD) model end-stage liver disease score is thought to be a good predictor of survival in individuals with advanced liver disease. Albumin, bilirubin, and platelets are all indicators of liver function in many chemistry lab tests. To find out the relationship between ALBi, PALBi, and FiB-4 are albumin-bilirubin (ALBi), platelet-albumin-bilirubin (PALBi), and fibrosis-4 (FiB-4) scores, accordingly. and MELD score-based mortality risk, as well as their presence in predicting cirrhosis mortality risk. Adults with liver disease were recruited for the analytic cross-sectional study. A positive association was discovered between ALBi, PALBi, and FiB-4 scores and MELD score. Based on MELD sensitivity and specificity values greater than the threshold, the ALBi, PALBi, and FiB-4 scores could predict mortality risk in cirrhosis **[15]**. Rui Zhang *et al*., (2020) studied the Effects of Anticoagulants on Experimental Models of Established Chronic Liver Diseases: A Systematic Review and Meta-Analysis**.** Anticoagulants' relevance in chronic liver disease is debatable. Treatment-related survival and antifibrotic benefits in chronic liver disease animal models. A effort is required for the literature was conducted to look for preclinical studies that looked at the anticoagulants' effects on chronic liver disease in animal models disease. The accuracy of the evidence and the quality of the procedures were also assessed. The data's outcomes were isolated and combined into random-effects models. Anticoagulants may decrease the severity of fibrosis investigated, portal pressure, inflammatory activity, and serum indices of hepatocellular damage in chronic liver disease animal models disorders, without affecting survival as The METAVIR score system is used to identify this. Experiments of high quality are still necessary **[16]**.

Shadrack Donkor *et al*., (2020) Aimed to study the Evaluation of the Acute Hepatoprotective Potential of Hydroethanolic Extract of Duranta erecta L. Parts . The objective of this study was to discover if hydroethanolic extracts of leaves, ripe and unripe fruits from Duranta erecta could protect rats against CCl4 and acetaminophen-induced hepatotoxicity. The mice were given CCl4 and acetaminophen to cause hepatotoxicity. The mice were given CCl4 and acetaminophen, which caused liver impairment, as demonstrated by increased ALP, ALT, AST, cGT and Levels of Bil, MDA, H2O2, and NO, as a change in liver microarchitecture. GSH, GPx, GST, and SOD are all antioxidants' levels increased after pre-treatment with

hydroethanolic extracts, notably from ripe Duranta erecta fruits. Improvements in liver structure backed up the biochemical findings. The findings imply that Duranta erecta ripe fruits hydroethanolic extract has hepatoprotective and antioxidative properties, in addition to the ability to reduce acetaminophen-induced toxicity, and could be utilised to treat drug-induced liver illnesses. CCL4 is an anti-inflammatory drug **[17]**. Manjot Kaur Gill *et al*., (2020) reviewed a Antitubercular Drug Induced Hepatotoxicity is an emerging medical problem. The antitubercular drugs are the leading cause of injury or damage to liver. Preventing drug-induced hepatotoxicity as a side effect of tuberculosis treatment has proven a difficult task. However, this causes treatment to be interrupted and the disease to resurface. The diverse mechanisms of antitubercular drug-induced hepatotoxicity, as well as its incidence and clinical management, were discussed . Anti-TB drugs have substantial side effects. medication is hepatotoxicity and by compromising treatment regimens it may reduce treatment effectiveness. The quadruple therapy medications INZ, RMP, and PZA are mostly metabolised by the liver and so may be hepatotoxic, resulting in disease recurrence or relapse. As a result, some natural or alternative choices that have been clinically proved should be employed to treat Anti-TB drugs cause hepatotoxicity. Ginger, garlic and honey are the most widely employed natural drugs for liver damage and hepatotoxicity in wide variety of patients **[18]**.

Divya Jain, Priya Chaudhary *et al*., (2020) reviewed the Hepatoprotective activity of medicinal plants: A mini review. Many plants and herbal mixtures have been proven to be in the treatment of hepatitis, it is quite successful. furthermore, In some cases, the treatment results are really not up to the mark. The experimental studies are carried out on a number of valuable plants and their formulations. Damage to the liver caused by chemicals in cell lines and animal models of liver cancer. Mostly liver damage is caused by the chemicals and oxidative stress mechanism. The aim of ethnopharmacological investigation in case of medicinal plants is not limited to find pure isolated compound as a therapeutic drug. Active fraction, extracts or mixture of extracts can be used as an effective drug option. The drugs obtained from plant (either individual or combination) for hepatic diseases are proved to be sufficient in the cure of hepatic diseases caused because of the intake of alcohol, viruses, and chemicals. Effective formulation is needed to be developed by the use of indigenous variety of plants, with all validation in terms of pharmacognostical experimentation and pre-clinical and

clinical investigations. In order to make plant drugs globally acceptable, the manufacturing of plant-based drugs should be governed properly according to the standard of efficacy or safety **[19]**. Birhanu Geta Meharie *et al*., (2020) evaluated the Hepatoprotective Activity Of The Crude Extract and solvent fractions of *Clutia Abyssinica* (Euphorbiaceous) leaf against CCL_4 of Induced hepatotoxicity in mice. Botanical agents are extensively employed in the treatment of liver illness, which are accompanied with a wide spectrum of side effects. *Clutia abyssinica* is the most extensively utilised herb in traditional medicine among these agents. The goal of this study was to examine if *Clutia abyssinica* leaves' crude 80 percent methanol extract and solvent fractions had any hepatoprotective qualities in mice. Indicators of liver injury include aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP)– and liver function such as total protein, albumin, and bilirubin were evaluated. The weight of the body and the weight of the liver were measured, as well as histopathologic examination and an antioxidant test in vitro against CCl4-induced hepatotoxicity. The aqueous fraction had no effect on the levels of any of the hepatocyte damage indicators. In the crude methanol extract and n-butanol fraction were able to reconstitute the 1,1-diphenylpicrylhydrazyl (DPPH) test method. hepatocyte hepatic architecture and scavenge free radicals. Because of its good safety profile, Clutia abyssinica has anti-oxidant action and could be a candidate for the development of hepatoprotective medicines **[20]**.

Christopher Trent Brewer *et al*., (2020) evaluated to study the Toxic proteomic Profiling of *hPXR* Transgenic Mice Treated with Rifampicin and Isoniazid. The same kind of hepatotoxicity caused by the hPXR and antitubercular medication systemic toxicity. Antitubercular medication isoniazid is used to treat a wide range of ailments of conditions including acute intermittent porphyria, anaemia, hepatotoxicity, hypercoagulable states, pellagra, vitamin B6 insufficiency, and peripheral neuropathy. The mechanism of rifampicin and isoniazid-induced liver and systemic damage in mPxr/ and hPXR mice treated with combinations of rifampicin and isoniazid was discovered using tandem mass tag mass spectrometry-based proteome screening. Cluster assembly machinery, cluster-containing proteins, cytochrome P450 enzymes, heme biosynthesis, homocysteine catabolism, oxidative stress responses, and vitamin B3 metabolism appear to be disrupted by antitubercular medication and vitamin B6 metabolism in the hPXR liver proteome, according to proteomic profiling analysis.

The new findings shed light on the aetiology a few of these procedures as well as potential targets for future research. The data can be found on ProteomeXchange under the PXD019505 identification **[21]**. Yuyan Zhou *et al*., (2020) Aimed to study the Arctiin Antagonizes Triptolide-Induced Hepatotoxicity via Activation of Nrf2 Pathway. Hepatotoxicity caused by TP has been limited in clinical studies Arctiin is an antioxidant that also protects the liver from oxidative damage. The protective role of arctiin In vitro and in vivo models were used to explore. Against TP-induced hepatotoxicity. The administration of arctiin reversed the experimental indexes. The findings revealed that arctiin could reduce TP-induced hepatotoxicity, and the molecular mechanism is most likely connected to its anti-oxidant properties **[22]**.

Lubna Danish *et al*., (2020) studied the Comparative Study of Protective Effect of Cimetidine and Verapamil on Paracetamol-Induced Hepatotoxicity in Mice .chemically Paracetamol is known as acetaminophen, if taken in higher doses has hepatotoxic potential. The aim of the research was to see if Cimetidine and Verapamil could protect the liver against damage paracetamol-induced damage. Additional groups were treated .In addition to the group receiving Cimetidine and Verapamil alone or both, the group receiving simply distilled water paracetamol. Histopathology and liver function testing demonstrated hepatotoxicity in the (PCM) paracetamol group, although normal parameters were seen in the Verapamil and Cimetidine groups. The findings strongly suggested that Cimetidine and Verapamil could protect the liver against paracetamol-induced damage **[23]**. Mohamed S. Othman *et al*., (2020) Aimed to study the Protective Effects of Melatonin on Aluminium-Induced Hepatotoxicity and Nephrotoxicity in Rats. Aluminium (Al) is a key denominator that has been associated with human and animal toxicity. The goal of this report was to look into the impact of melatonin (MEL) in rat hepatotoxicity and nephrotoxicity after exposure to aluminium chloride ($AlCl_3$). MEL therapy reduced LPO and NO levels while increasing GSH levels. When MEL was given before $AlCl_3$, the antioxidant activity enzymes GPx, SOD, CAT, and GR were all tested. All restored at the same time. Melatonin also inhibited $AlCl_3$'s apoptotic effect by increasing Expression of the Bcl-2 protein in the liver and kidney and lowering proinflammatory cytokine expression. The protective impact MEL's ability to protect against $AlCl_3$ toxicity was supported by histopathological results in the tissues of the liver and kidneys. MEL appears to

protect against $AlCl_3$ toxicity by increasing the antioxidant defence system **[24]**.

Nerdy Nerdy, Kiking Ritarwan (2020) Investigated the Hepatoprotective Activity and Nephroprotective Activity of Peel Extract from Three Varieties of the Passion Fruit (Passiflora Sp.) in the Rats that are albino. The purpose of this study is to test the hepatoprotective and nephroprotective properties of three kinds of passion fruit in albino rats using scientific methods (gentamicin-induced nephrotoxicity) (Rattus norvegicus.) The hepatoprotective efficacy was determined by comparing the liver biochemical (AST and ALT) responses to paracetamol (a hepatotoxic drug) after ten days of extract therapy. Based on Nephroprotective, With gentamicin (a nephrotoxic medication), the kidney biochemical (urea and creatinine) assay was performed) induced after the treatment with extract was done. Based on the extracts, hepatoprotective and nephroprotective action was observed, with dose-dependent efficacy. Peel of purple passion fruit extract was compared to red passion fruit peel extract and yellow passion fruit peel extract for nephroprotective and hepatoprotective effects **[25]**. Evan Prince Sabina *et al*., (2019) studied the comparison of hepatoprotective activity of Bacoside to Silymarin treatment against a combined Isoniazid and Rifampicin-induced hepatotoxicity. Rifampicin and isoniazid are two medications used to treat tuberculosis, although they have different side effects and hepatotoxicity risks. Because the metabolism of isoniazid (INH) and rifampicin (RIF) takes place in the liver, hepatotoxicity is the main reason for their continued usage. Bacoside is derived from the *Bacopa monnieri* plant that has been produced and used as a nerve tonic, antioxidant, and free radical scavenger. In rats, INH-RIF caused hepatotoxicity can be countered by retaining hepatocyte membrane integrity. Silymarin is a medication that has low toxicity and no drug interactions. It's used to treat various diseases, a variety of medically verified hepatic diseases. This study objective is to investigate to see if Bacoside could protect Wistar albino rats' livers against INH and RIF-induced damage. Bodyweight, liver enzyme indicators, liver antioxidant, and liver histology were all examined in this study. INH- and RIF-treated rats had anomalies in liver markers that were normal when they were given Bacoside, which is identical to what the normal control and Silymarin-treated groups had. Bacoside's hepatoprotective efficacy protected Wistar albino rats against INH and RIF-induced toxicity was revealed in this work **[26]**.

Yalew Molla *et al*., (2019) Aimed to study the anti-tubercular drugs induced

hepatotoxicity Associated Factors among Tuberculosis Patients at Selected Hospitals, Ethiopia . The study's prospective cross-sectional design was undertaken by obtaining blood samples from new TB patients in three hospitals to measure the rise of liver proteins indicating liver damage from the outset of starting medication. At a statistically significant degree of evidence threshold of P0.05, factors that identified drug-induced hepatotoxicity were used in a multivariate logistic regression followed by binary logistic regression analysis. In tuberculosis patients on first-line anti-tuberculosis treatments, hepatotoxicity is common. To reduce the severity of drug-induced hepatotoxicity, patients with advanced age, comorbid diseases, and extrapulmonary tuberculosis should have their liver function checked on a regular basis. Extrapulmonary tuberculosis diagnosis, concomitant condition, and advanced age are all linked to first-line antituberculosis drug-induced hepatotoxicity (P0.05) **[27]**. mahdi m thuawaini *et al*., (2019) studied the hepatoprotective and nephroprotective effects of the aqueous extract of turmeric (*Curcuma longa*) in rifampicin and isoniazid-induced hepatotoxicity and nephrotoxicity in rats. The aim of the research was to see how oral administration of aqueous turmeric extract affected the results. Affected isoniazid and rifampicin-induced in rats, hepatotoxicity and nephrotoxicity were observed. (RIF). It was calculated using estimates liver and kidney disease functioning, as well as histological alterations. Enzymatic testing was used to detect kidney and liver function markers (aspartate transaminase [AST], alanine transaminase [ALT], alanine phosphatase [ALP], bilirubin, blood urea, and creatinine). Furthermore, the liver and renal tissues were examined. promptly separated and fixed in 10% formalin before being exposed to histological investigations. A statistical analysis was performed using the t-test. The turmeric extract has hepato- and reno-protective properties in rats suffering from hepato- and reno-toxicity caused by RIF and INH. Treatment with RIF and INH resulted in a considerable decrease in serum AST, ALT, Total bilirubin, ALP, creatinine, urea, and total protein levels are all examined. Histopathological and biochemical results were used to confirm the results of the subsequent tests **[28]**.

Maryem Ben Salem *et al*., (2019) evaluated the LC-MS/MS Analysis and Hepatoprotective Activity of Artichoke (*Cynara scolymus* L.) Leaves Extract against High Fat Diet-Induced Obesity in Rats *Cynara scolymus* L. (Artichoke) The drug has been employed in the treatment metabolic problems. The objective of this research was to see if *Cynara scolymus* leaf extract could protect rats' livers from a

high-fat diet (HFD). The antihypercholesterolemic and antioxidative properties in vivo of *Cynara scolymus* leaves extract contains the highest abundant phenolic components were evaluated. Based on the lipid profile that was measured, the oxidative stress system. It was discovered in liver tissue. HFD-induced hepatic dysfunction was demonstrated AST, ALT, ALP, and LDH values that are extremely abnormal, according to the findings. The addition of EEA to the diet lowered serum lipid profiles and hepatic diseases, supporting the histology findings by lowering fatty liver deposits in the hepatic lobule. In HFD-induced obese mice, the data imply that Cynara leaves have antiobesity and antioxidant liver benefits. The ethanol extract of *Cynara scolymus* leaves has a possible effect on rats who have been fed a high fat-rich diet. Cynara extract, which is abundant in antioxidants, reduces the negative effects of a high-fat diet on cholesterol accumulation and hepatic diseases **[29]**. Dalia Fouad *et al*., (2019) estimated the Hepatoprotective activity of raspberry ketone is mediated via inhibition of the NF-κB/TNF-α/ caspase axis and mitochondrial apoptosis in chemically induced acute liver injury. CCl4 also induced the expression of inflammatory cytokines (NF-κB and TNF-α). The lowering of liver enzymes demonstrated raspberry ketone's hepatoprotective effect. Furthermore, RK pre-treatment reduced CCl_4-induced inflammatory mediator overexpression. Caspases are down, and cytoplasmic cytochrome-C expression is down, and suppression of DNA fragmentation were all signs of raspberry ketone antiapoptotic action. RK is a hepatoprotective medication with a lot of promise, according to the current investigation. Antioxidant, anti-inflammatory, and anti-apoptotic actions are among the underlying processes. To our knowledge, this is the first study to show the hepatoprotective efficacy of RK protects the liver against CCl_4-induced damage. RK had dose-dependent cytoprotective effects against CCl_4-induced liver damage. Our findings show that RK protects the liver of rats from CCl_4-induced injury and could be used as a preventive anti-oxidant against hepatotoxicity **[30]**.

Henna Sood *et al*., (2019) Scientific validation of the antimicrobial and antiproliferative potential of *Berberis aristata* DC root bark. The optimum organic solvent for evaluating the probable chemical responsible for antibacterial action was discovered to be ethyl acetate. Diterpenes are now the most prevalent phytoconstituents, with antibacterial the range of activity is 16.66 to 42.66 mm. The concentration of minimal inhibitory

concentration that was found to be the lowest was found in ethyl acetate extract, followed by diterpenes and flavonoids. Biosafety was determined using the Ames and MTT assays. Diterpenes' in vitro cytotoxicity against L20B, RD, and Cell lines from Hepatitis 2 indicated IC50 values varying between 245 and 473 g/mL. Diterpenes' acute oral toxicity in Swiss albino mice had no effect on their behaviour, body weight, metabolic markers, or organ architecture. Because of this the antibacterial capability and biosafe profile, the current study suggests that B. aristata could be going to better use a powerful medication **[31]**. Mohamed M. Abdel-Daim *et al*., (2019) aimed to study the Piperine Enhances the Antioxidant and Anti-Inflammatory Activities of Thymoquinone against Microcystin-LR-Induced Hepatotoxicity and Neurotoxicity in Mice**.** Microcystin (MC-) LR is a common cyanotoxin produced by the cyanobacterium Microcystis aeruginosa in contaminated freshwater environments. Humans and animals are both at risk from microcystin. The purpose of the study was to see if thymoquinone (TQ) and/or piperine (PI) are present (PP) could help mice with MC toxicity. The findings demonstrated that MC caused hepatotoxicity and neurotoxicity as a consequence increased blood AST, ALP, ALT, GT, LDH, IL-1, IL-6, and TNF-levels. As a result, MC raised MDA and NO levels in the liver and brain while lowering GSH, SOD, CAT, and GSH-Px are all antioxidants' levels. The liver's and brain's electron transport chains could be a potential target for MC. TQ and/or PP reduced the oxidative stress caused by MC, which could be due to their antioxidant capabilities. Because of the PP-enhanced bioavailability of TQ, the concurrent therapy of TQ and PP were discovered to be the optimum regimen **[32]**.

Hassan Farghali *et al*., (2019) evaluated the SIRT1 Modulators in Experimentally Induced Liver Injury. The goal of this research is to emphasise the role SIRT1 is an endogenous stress sensor. as a potential contributor in hepatoprotection. SIRT1 expression by liver injury indicators had an inverse connection. SIRT1's cytoprotective properties are shown within a certain range of expression. SIRT1 is a component of hepatoprotective actions of polyphenols, where SIRT1 inhibitors stop SIRT1 to do its function, and allosteric SIRT1 inhibitors stop SIRT1 doing its work. activators, based on their catalytic activity, imitate the hepatoprotective benefits of polyphenols. As a result, we suggest that pharmacologic regulation of SIRT1 could be a significant a stage in the therapy xenobiotic-induced hepatotoxicity and a potential major stride in the treatment of hepatic injuries **[33]**. Myoung-Sook Shin *et al*., (2019) aimed to

study A Hydroxypropyl Methylcellulose-Based Solid Dispersion of Curcumin with Enhanced Bioavailability and Its Hepatoprotective Activity. Curcumin is a polyphenol chemical *Curcuma longa* is the source of this extract. rhizomes that have antioxidant, anti-inflammatory, anticancer, and antibacterial activities. Using a model of tert-butyl hydroperoxide (t-BHP)-induced hepatocyte injury, the therapeutic efficacy as a hepatoprotective drug was studied. The activity of DW-CUR 20 reduced apoptosis-related proteins such Poly (ADP-ribose) polymerase and inhibited lactate dehydrogenase release. The DW-CUR 20 formulation could be a potential way to boost curcumin's medicinal efficacy while also improving its safety **[34]**.

Xue He *et al*., (2019) studied the Protective effect of pyrrolidine dithiocarbamate on isoniazid/rifampicin-induced liver injury in rats. Anti-tuberculosis (TB) medications such as Rifampicin with isoniazid (inH) (riF) remain first-line treatments. Nuclear factor-B (nF-B) plays a critical function in regulating immunity and inflammation, and the medications used in conjunction with hepatotoxicity with nuclear factor-B (nF-B) play a significant role in regulating immunity and inflammation. The goal of this research was to see if PdTc's inH/riF-induced protective effects and mechanisms on liver injury. Pyrolidine dithiocarbamate (PdTc), an inhibitor of nF-B, has been shown to keep the liver healthy from acute and chronic damage. To compare biochemical markers of the liver histopathological damage in the serum, oxidative stress, nF-B activity, mRNA expression in the liver tumour necrosis factor (TnF)-, pump for bile salt export (BSeP), and the expression of proteins BSeP, PdTc was injected intraperitoneally 2 hours after inH and riF have been co-administered. The inhibition of nF-B activation by PdTc therapy significantly reduced biochemical and histological damage to the liver, reduced oxidative stress, and reversed declines in BSeP, TnF-mrna levels, and protein expression caused by inH and riF co-administration. According to the present evidence, inH/riF-induced liver damage is dependent **[35]**.

D.Menzies *et al*., (2018) estimated the Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults. In tuberculosis patients who have a latent infection, a 9-month isoniazid treatment can prevent active tuberculosis. The regimen, on the other hand, has been associated with low adherence and hazardous side effects. Adults infected with latent TB were randomly assigned to undergo therapy with a rifampicin or isoniazid regimen following randomization in an open-label trial conducted in nine countries for the prevention of proven

active TB. The terms "noninferiority" and "potential superiority" were used to evaluate. Clinically confirmed active tuberculosis, grade 3–5 adverse events, as well as the completion of the treatment plan were all secondary outcomes. For the purpose of preventing active tuberculosis, a 4-month rifampicin regimen was not inferior to a 9-month isoniazid regimen, and it was linked to a greater rate of treatment completion and improved safety **[36]**.

Zhuoling An *et al*., (2018) aimed to study Metabolomics of Hydrazine-Induced Hepatotoxicity in Rats for Discovering Potential Biomarkers Metabolic pathway disturbances associated with liver damage caused by drugs remain unsatisfactory. The hepatotoxicity diagnostic research was utilised to reduce drug-induced liver injury and improve clinical safety. To find possible biomarkers for hydrazine-induced hepatotoxicity, researchers used a metabolomics technique that included Multivariate statistics and rapid-resolution liquid chromatography/tandem mass spectrometry (RRLC-MS/MS) studies. Statistical data analyses and receiver operating characteristic (ROC) curves were performed to identify the most significantly changed metabolites. The metabolomics pathway shown that the production of phenylalanine, tyrosine, and tryptophan, showed substantial interactions with hydrazine-induced liver damage, as well as tyrosine metabolism. The discriminating metabolites may be valuable in deciphering the pathogenic mechanisms of liver injury and may offer good possibilities for clinically diagnosing drug-induced liver harm **[37]**. S.Sylvester Darvin *et al*., (2018) studied the Hepatoprotective effect of lawsone on rifampicin-isoniazid induced hepatotoxicity in in vitro and in vivo models . Using in vivo and in vitro methods, the efficiency of lawsone as a hepatoprotective agent, the primary bioactive naphthoquinone found in *Lawsonia inermis* L. (Lythraceae), was demonstrated. Using the ABTS assay, the antioxidant action of lawsone was assessed. The task at hand RIF-INH treated HepG2 cells were used to test lawsone's hepatoprotective activity. The RIF-INH-treated rats were given lawsone, which drastically reduced serum transaminases levels. The albumin-to-globulin ratio was improved, and bilirubin levels were reduced. The hepatoprotective effect of lawsone was discovered in a study; more research will provide a better knowledge of how lawsone Hepatoprotection is possible **[38]**.

Saifei Lei *et al*., (2018) studied the Clinical perspectives of isoniazid-induced liver injury .Isoniazid (INH) is an anti-mycobacterial tuberculosis drug that can be used to treat both active and latent

tuberculosis (TB). In clinical practise, INH has been administered for many years and is still widely used in anti-TB treatment. The hepatotoxic effects of INH are discussed in this paper, as well as their applicability and mechanism in predicting and preventing INH hepatotoxicity in clinical practise. INH toxicity is still a safety concern in clinical practise, and there are no mechanism-based treatments to forecast, prevent, or cure it. To analyse and address the unanswered questions and underlying processes of INH hepatotoxicity, clinical and pre-clinical investigations using cutting-edge technology are required **[39]**. G. V. Zodape and P. P. Bhise (2018) studied the Effect of aloe vera extract and isoniazid - rifampicin drug on liver histological studies of male wistar rats . The purpose of this research was to see if Aloe vera extract may reduce the toxicity caused by INH - RIF in male Wistar albino rats. Studies on histological alternations were shown using two different methodologies. SEM microscopy was used to further process the same tissues and compound microscopy. It was discovered that Aloe vera extract, isoniazid, and rifampicin had an influence on the histological architecture of the liver. Partially restored hepatic function, as evidenced by normalisation of serum liver function markers, and hepatoprotection against INH+RIF-induced hepatotoxicity, as demonstrated by the partial reversal of increased serum transaminases, which returned to normal (but only partially) after supplementation with Aloe vera, indicating a partial hepatoprotective effect. Anti-tuberculosis medicines and aloe vera extract co-administration of INH-RIF medications resulted in some hepatoprotection **[40]**.

Maiti Swatilekha *et al*., (2018) studied the Hepatotoxic effect of Rifampicin as an Anti-Tuberculosis drug on male Albino rat. Tuberculosis one of the most hazardous infections spread through the air. Rifampicin is an antituberculosis medication that causes hepatotoxicity. The liver regulates the detoxification process while maintaining metabolic balance. Several biochemical markers to determine toxicity in the treatment group vs the control group such as serum glutamate pyruvate transaminase (AST), serum glutamate oxaloacetate transaminase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), serum total protein, serum bilirubin, and serum cholesterol were employed. Because the chosen dose of rifampicin is hepatotoxic, tuberculosis patients must be closely monitored and cared for during treatment. Rifampicin, an antituberculosis medicine, affects serum protein, serum bilirubin, MDA content, Activity of the enzymes AST, ALT, ALP, and LDH. There are no alternative

medicines for tuberculosis treatment besides these antibiotics. As a result, thorough monitoring and care must be provided throughout tuberculosis therapy **[41]**. Geetha. Nair *et al*., (2018) aimed to study the Hepatoprotective effect of *Asystasia chelonoides* var. *Chelonoides nees*. (Acanthaceae) leaf extracts against In Wistar rats, CCl_4 caused liver damage. The focus of this research was to see if an ethanolic extract of *Asystasia chelonoides* var. chelonoides could prevent and cure CCl_4-induced liver damage in Wistar rats at different dose levels. Evaluation of hepatic damage biochemical markers such ALT, AST, ALP, GGT, SB, TGL, TC, and TP are some of enzymes, as well as calculation of liver tissue antioxidant status (SOD, CAT, GSH, and MDA levels) and histological evaluation. Histopathological investigation of drug-treated rats corroborated the plant's hepatoprotective activity. In Wistar rats, leaf extract has strong preventive and hepatoprotective effect in the case of CCl_4-induced liver damage **[42]**.

Nasir Aziz Wagay *et al*., (2018) evaluated the latest study created the goal of analysing the phytoconstituents of *Neptunia triquetra* (Vahl) Benth. The anti-inflammatory and hepatoprotective properties of ethanol (EE), chloroform (CE), and dichloromethane (DCME) stem extracts were investigated. GC-HRMS was used to examine the extracts for phytoconstituents. Anti-inflammatory activity was used to access CE, EE, and DCME utilising oedema caused by carrageenan, granuloma caused by cotton pellets, and the carrageenan-induced air-pouch model. Biochemical markers in serum (AST, ALT, ALP, GGT, total lipids, and total protein) and liver were used to assess hepatotoxicity. The findings reveal that N. triquetra stem has a greater hepatoprotective impact than silymarin, and that the anti-inflammatory reaction is comparable to or lower than indomethacin **[43]**. Fatma Abd-elkader Moharram *et al*., (2018) evaluated the Phenolic profile, anti-inflammatory, antinociceptive, anti-ulcerogenic and hepatoprotective activities of *Pimenta racemose* leaves. The phenolic contents of an Aqueous methanol extract (AME) of leaves at 80% are studied, in addition to biological activities of the extract. UV, NMR, and UPLC-ESI-MS spectroscopy were used to identify the chemicals. paw oedema caused by carrageenan Chemical and thermal stimuli were used to assess anti-inflammatory activity, whereas chemical and thermal stimuli were used to assess antinociceptive activity. The anti-ulcerogenic effect of AME was tested against stomach injury. Hepatoprotective action was also studied by measuring Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are two enzymes that help the body

break down amino acids (AST) after paracetamol administration. Histopathological tests confirmed both anti-ulcerogenic and hepatoprotective effects. AME reduced stomach mucosal lesions compared to the ranitidine group and the ethanol control group, ALT at three doses, and AST compared to paracetamol, indicating a prospective anti-inflammatory efficacy by regulation of oedema and antinociceptive activity by reduction in the frequency of writhes. It was established from histopathological examinations that phenolic compounds were abundant in *P.racemose* leaves and had substantial biological activities **[44]**.

Heng Zhou *et al*., (2018) evaluated the study of enhanced Regeneration and Hepatoprotective Effects of Interleukin 22 Fusion Protein on a Predamaged Liver Undergoing Partial Hepatectomy Liver ischemia-reperfusion injury (IRI). Interleukin 22 (IL-22), a hepatocyte-derived factor, is critical for hepatoprotection and regeneration after hepatectomy. Treatment with IL-22-FP reduced liver damage and increased hepatocyte proliferation. IL-22-FP stimulated the liver signal transducer and activator of transcription 3 (STAT3) and elevated the production of several mitogenic proteins after being administered. Ischemia-reperfusion injury reduced liver damage by lowering aminotransferase levels and improving the histology of the liver. As a result, IL-22-FP enhances liver regeneration and reduces IRI-induced Damage to the liver in mice with pre-damaged livers following PHx. In individuals who have undergone PHx, we believe that IL-22-FP. It's possible that this is a promising treatment. medication for regeneration deficit and liver IRI **[45]**. Julfikar Ali Junejo Ignat *et al*., (2018) studied the Exploration of antioxidant, antidiabetic and hepatoprotective activity of *Diplazium esculentum*. The hydroalcoholic extract of *Diplazium esculentum* leaf, a wild edible plant native to India's northeast, is being studied for phytochemical and medicinal purposes (DEHAe). Griess reagent was used to determine Nitric oxide and the DPPH test inhibition. The amount of antioxidant activity was calculated. Streptozotocin (STZ) was induced artificially. The effect of DEHAe on fasting glucose, lipid profile, biochemical parameters, affects the action of antioxidant enzymes was studied. Carbon tetrachloride (CCl_4) caused liver damage method was used to assess hepatoprotective activity. Pancreas histology slides were used to keep an eye on the histological changes. The plant extract's projected activity in an animal model. DEHAe's IC50 value for in vitro antioxidant and NO inhibition activity was discovered. On rats pre-treated with DEHAe, CCl_4 had only a little effect on

total bilirubin and hepatic enzyme activity. The pancreas of DEHAe-treated mice revealed a considerable decrease in necrosis and b-cell regeneration. DEHAe exhibits considerable free radical scavenging, antidiabetic, hyperlipidaemic, and hepatoprotective action, according to the current study, and so can be taken as a functional vegetable **[46]**.

Liliana Torres González *et al*., (2017) aimed to study the in vitro assessment of hepatoprotective agents against damage induced by acetaminophen and CCl_4. The hepatoprotective effects were evaluated using plant extracts. The aim of the research is to see if hepatoprotective drugs can protect HepG2 cells from the damage caused Paracetamol with carbon tetrachloride (CCl_4). Plant extracts were used to test the hepatoprotective properties. An assay for 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging was used to determine antioxidative activity. Cell viability, Cell viability, enzyme activity, lipid peroxidation, TAOxC, and SOD and GSH levels were all affected by CCl_4, as were the activities of aspartate aminotransferase (AST), lactate dehydrogenase (LDH), alanine aminotransferase (ALT), and total antioxidant capacity (TAOxC); and reduced glutathione (GSH), superoxide dismutase (SOD), and lipid peroxidation. The APAP was more consistent in generating cell damage with CCl_4. Only SLB provides hepatoprotection. The levels of LDH, AST, and MDA were all good indicators of liver injury **[47]**. Mirza Kalam Urfi *et al*., (2017) aimed to study the Role of *Tamarix gallica* Leaves Extract in Liver Injury Induced by Rifampicin Plus Isoniazid in Sprague Dawley Rats. The hepatoprotective potential of *Tamarix gallica* leaf extract (TGLE) was tested for its ability to protect against rifampicin (RIF) and isoniazid (INH)-induced liver impairment. Under light anaesthesia, the blood was drawn from the sacrificed animals through the retro-orbital plexus, and serum was separated. For histological tests, 10 percent formaldehyde was used to fix the appropriate amount of separated liver tissue. Elevated blood bilirubin, aspartate transaminase, Lactate dehydrogenase, alkaline phosphatase, and cholesterol levels dropped, but the levels of total protein and albumin increased. and serum marker enzyme levels returned to normal, indicating protection against liver injury. In experimental rats, the leaves extract has shown to have hepatoprotective properties against RIF plus INH-induced liver injury **[48]**.

Sandra Doß *et al*., (2017) aimed to study the Hepatotoxicity of Antimycotics Used for Invasive Fungal Infections: In Vitro Results. Drug-induced liver damage is currently the most serious concern.

Different doses of cytotoxicity the antimycotics used for systemic infections on hepatocytes was studied in a standardised assay. The viability of albumin synthesis, cytochrome 1A2 activity, and cell death were all assessed after incubation. For statistical analysis, Kruskal-Wallis and Mann–Whitney tests were utilised. Antimycotics, particularly azoles, which are used to treat systemic infections, should be used with caution in patients who have liver failure, insufficiency, or are at high risk for it; consequently, therapeutic drug monitoring should be considered. More research using this method is encouraged **[49]**. Deng-Ke Li, *et al*., (2017) aimed to study the Hepatotoxicity in Rats Induced by Aqueous Extract of *Polygoni Multiflori* Radix, Root of *Polygonum multiflorum* Related to the Activity Inhibition of CYP1A2 or CYP2E1. The objective of this research is to see if there's a link between *Polygoni Multiflori* Radix-induced hepatotoxicity and CYP1A2 or CYP2E1 activity in the liver of rats. After injection of a particular inhibitor for CYP2E1 or CYP1A2 combined with aqueous extract administration of PMR, the levels of ALT and AST levels were abnormally high and dramatically lowered, especially when the treatment was repeated over time intervals. The histological examination revealed that rats getting Treatment of PMR with CYP1A2 or CYP2E1 activity blocked suffered moderate liver damage, but PMR therapy was given to rats using a CYP inhibitor alone had no significant liver damage. The hepatotoxicity caused by PMR in clinical trials is largely due to the reduced according to CYP1A2 or CYP2E1 activity to genetic variation **[50]**.

DISCUSSION

The investigators, participants, and statistician were all unaware of the treatment allocation **[1]**. Diagnostic indicators changed when melittin was given; haematological alterations were substantially higher in Melittin groups than in the dangerous group **[2]**. When compared to a placebo, *P.niruri* improved total antioxidant levels while also stimulating appetite **[3]**. Methotrexate protects the liver through antioxidant, anti-inflammatory, and anti-apoptotic mechanisms, MTX toxicity is reduced **[4]**.

CONCLUSION

We conclude from the above-mentioned literature that it will be useful to young researchers in furthering their studies. On the basis of data base access, additional research can be done.

ACKNOWLEDGEMENT: We acknowledge Chalapathi Institute of Pharmaceutical Sciences (Autonomous) for their service.

CONFLICTS OF INTEREST: Authors declare no conflict of interest.

REFERENCES

[1] Babaei A, Taghavi SA, Mohammadi A, Mahdiyar MA, Iranpour P, Ejtehadi F, *et al*. Comparison of the efficacy of oral fenugreek seeds hydroalcoholic extract versus placebo in nonalcoholic fatty liver disease; a randomized, triple-blind controlled pilot clinical trial. Indian J Pharmacol, Volume 52, Issue 2, 2013, pp. 86-93

[2] Naji, Khalid Mohammed, *et al*. "Hepatoprotective Activity of Melittin on Isoniazid- and Rifampicin-Induced Liver Injuries in Male Albino Rats." BMC Pharmacology and Toxicology, vol. 22, no. 1, 2021, p. 39, doi:10.1186/s40360-021-00507-9

[3] Sowjanya K, Girish C, Bammigatti C, Prasanna Lakshmi NC. Efficacy of *Phyllanthus niruri* on improving liver functions in patients with alcoholic hepatitis: A double-blind randomized controlled trial. Indian J Pharmacol ,Volume 53, Issue 6, 2021, pp. 448–56

[4] Mohamed M, El Sheikh AK, Mohammed HH. Modulation of liver P-glycoprotein expression may contribute to gossypin protection against methotrexate-induced hepatotoxicity. Indian J Pharmacol ,Volume 53, Issue 1, 2021, pp. 25–30

[5] Ignat, Maria Valentina, *et al*. "Plants of the Spontaneous Flora with Beneficial Action in the Management of Diabetes, Hepatic Disorders, and Cardiovascular Disease." Plants, vol. 10, no. 2, 2021, p. 216, doi:10.3390/plants10020216

[6] Gök, Hasya Nazlı, *et al*. "Preclinical Study on the Hepatoprotective Effect of Pollen Extract of *Pinus Brutia* Ten. (Red Pine) in Mice and Phenolic Acid Analysis." Turkish Journal of Pharmaceutical Sciences, vol. 18, no. 3, 2021, pp. 319–325, doi:10.4274/tjps.galenos.2020.47154

[7] Paudel, Kiran, *et al*. "REVIEW ON HEPATOPROTECTIVE EFFECT OF *Berberis aristata* DC." International Ayurvedic Medical Journal, vol. 09, no. 1, 2021, pp. 190–199, doi:10.46607/iamj.3109012021

[8] Su, Qiang, *et al*. "Antituberculosis Drugs (Rifampicin and Isoniazid) Induce Liver Injury by Regulating NLRP3 Inflammasomes." Mediators of Inflammation, vol. 2021, 2021, p. 8086253, doi:10.1155/2021/8086253

[9] Ielciu, Irina, *et al*. "Evaluation of Hepatoprotective Activity and Oxidative Stress Reduction of *Rosmarinus Officinalis L.* Shoots Tincture in Rats with Experimentally Induced Hepatotoxicity." Molecules (Basel, Switzerland), vol. 26, no. 6, 2021, p. 1737, doi:10.3390/molecules26061737

[10] Cao, Dan, *et al*. "Combined Metabolomics and Network Toxicology to Explore the Molecular Mechanism of *Phytolacca Acinose Roxb*-Induced Hepatotoxicity in Zebrafish Larvae in Vivo." Evidence-

Based Complementary and Alternative Medicine: *ECAM*, vol. 2021, 2021, p. 3303014, doi:10.1155/2021/3303014

[11] Jaeschke, Hartmut, *et al*. "Recommendations for the Use of the Acetaminophen Hepatotoxicity Model for Mechanistic Studies and How to Avoid Common Pitfalls." Acta Pharmaceutica Sinica. B, vol. 11, no. 12, 2021, pp. 3740–3755, doi:10.1016/j.apsb.2021.09.023

[12] Pondugula, Satyanarayana R., *et al*. "A Clinically Relevant Combination Treatment with Doxorubicin and Cyclophosphamide Does Not Induce Hepatotoxicity in C57BL/6J Mice." Liver Research, vol. 5, no. 4, 2021, pp. 239–242, doi:10.1016/j.livres.2021.04.002

[13] Wang, Yukun, and Xuebo Chen. "Joint Decision-Making Model Based on Consensus Modeling Technology for the Prediction of Drug-Induced Liver Injury." Journal of Chemistry, vol. 2021, 2021, pp. 1–20, doi:10.1155/2021/2293871

[14] Brecklinghaus, Tim, *et al*. "The Hepatocyte Export Carrier Inhibition Assay Improves the Separation of Hepatotoxic from Non-Hepatotoxic Compounds." Chemico-Biological Interactions, vol. 351, no. 109728, 2022, p. 109728, doi:10.1016/j.cbi.2021.109728

[15] Sindhughosa, D. A., *et al*. "Evaluation of Mortality Risk in Liver Cirrhosis with Albumin- Bilirubin (Albi), Platelet-Albumin-Bilirubin (Palbi), and Fibrosis-4 (Fib-4) Scores." Biomedical & Pharmacology Journal, vol. 14, no. 02, 2021, pp. 985–991, doi:10.13005/bpj/2200

[16] Zhang, Rui, *et al*. "Effects of Anticoagulants on Experimental Models of Established Chronic Liver Diseases: A Systematic Review and Meta-Analysis." Canadian Journal of Gastroenterology & Hepatology, vol. 2020, 2020, p. 8887574, doi:10.1155/2020/8887574

[17] Donkor, Shadrack, *et al*. "Evaluation of the Acute Hepatoprotective Potential of Hydroethanolic Extract of *Duranta Erecta L.* Parts." Journal of Toxicology, vol. 2020, 2020, p. 8815719, doi:10.1155/2020/8815719

[18] Antitubercular Drug Induced Hepatotoxicity: A Review. European Journal of Molecular & Clinical Medicine, Volume 7, Issue 7, 2020, pp. 2840-2847

[19] Jain, Divya, *et al*. "Hepatoprotective Activity of Medicinal Plants: A Mini Review." Journal of Medicinal Plants Studies, vol. 8, no. 5, 2020, pp. 183–188, doi:10.22271/plants.2020.v8.i5c.1212

[20] Meharie, Birhanu Geta, *et al*. "Evaluation of Hepatoprotective Activity of the Crude Extract and Solvent Fractions of *Clutia Abyssinica* (Euphorbiaceae) Leaf against CCl4-Induced Hepatotoxicity in Mice." Journal of Experimental

Pharmacology, vol. 12, 2020, pp. 137–150, doi:10.2147/JEP.S248677

[21] Brewer, Christopher Trent, *et al*. "Toxicoproteomic Profiling of HPXR Transgenic Mice Treated with Rifampicin and Isoniazid." Cells (Basel, Switzerland), vol. 9, no. 7, 2020, p. 1654, doi:10.3390/cells9071654

[22] Zhou, Yuyan, *et al*. "Arctiin Antagonizes Triptolide-Induced Hepatotoxicity via Activation of Nrf2 Pathway." BioMed Research International, vol. 2020, 2020, p. 2508952, doi:10.1155/2020/2508952

[23] Danish, Lubna, *et al*. "Comparative Study of Protective Effect of Cimetidine and Verapamil on Paracetamol-Induced Hepatotoxicity in Mice." International Journal of Hepatology, vol. 2020, 2020, p. 9185361, doi:10.1155/2020/9185361

[24] Othman, Mohamed S., *et al*. "The Protective Effects of Melatonin on Aluminum-Induced Hepatotoxicity and Nephrotoxicity in Rats." Oxidative Medicine and Cellular Longevity, vol. 2020, 2020, p. 7375136, doi:10.1155/2020/7375136

[25] Nerdy, Nerdy, and Kiking Ritarwan. "Hepatoprotective Activity and Nephroprotective Activity of Peel Extract from Three Varieties of the *Passion Fruit* (Passiflora Sp.) in the Albino Rat." Open Access Macedonian Journal of Medical Sciences, vol. 7, no. 4, 2019, pp. 536–542, doi:10.3889/oamjms.2019.153

[26] Sabina EP, Peter S J, S P, Geetha A. A comparison of hepatoprotective activity of Bacoside to *Silymarin* treatment against a combined Isoniazid and Rifampin-induced hepatotoxicity in female Wistar rats. J Histotechnol, Volume 42, Issue 3, 2019, Pages 128–36 http://dx.doi.org/10.1080/01478885.2019.1638535

[27] Molla, Yalew, *et al*. "Anti-Tuberculosis Drug Induced Hepatotoxicity and Associated Factors among Tuberculosis Patients at Selected Hospitals, Ethiopia." Hepatic Medicine: Evidence and Research, vol. 13, 2021, pp. 1–8, doi:10.2147/HMER.S290542

[28] M Thuawaini, Mahdi, *et al*. "Hepatoprotective And Nephroprotective Effects Of The Aqueous Extract Of *Turmeric (Curcuma Longa)* In Rifampicin And Isoniazid-Induced Hepatotoxicity And Nephrotoxicity In Rats." Asian Journal of Pharmaceutical and Clinical Research, 2019, pp. 293–298, doi:10.22159/ajpcr.2019.v12i3.30419

[29] Ben Salem, Maryem, *et al*. "LC-MS/MS Analysis and Hepatoprotective Activity of *Artichoke (Cynara Scolymus L.)* Leaves Extract against High Fat Diet-Induced Obesity in Rats." BioMed Research International, vol. 2019, 2019, p. 4851279, doi:10.1155/2019/4851279

[30] Fouad, Dalia, *et al*. "Hepatoprotective Activity of Raspberry Ketone Is Mediated via Inhibition of the NF-KB/TNF-α/Caspase Axis and Mitochondrial Apoptosis in Chemically Induced Acute Liver Injury." Toxicology Research, vol. 8, no. 5, 2019, pp. 663–676, doi:10.1039/c9tx00068b

[31] Sood, Henna, *et al*. "Scientific Validation of the Antimicrobial and Antiproliferative Potential of *Berberis Aristata DC* Root Bark, Its Phytoconstituents and Their Biosafety." *AMB Express*, vol. 9, no. 1, 2019, p. 143, doi:10.1186/s13568-019-0868-4

[32] Abdel-Daim, Mohamed M., *et al*. "Piperine Enhances the Antioxidant and Anti-Inflammatory Activities of Thymoquinone against Microcystin-LR-Induced Hepatotoxicity and Neurotoxicity in Mice." Oxidative Medicine and Cellular Longevity, vol. 2019, 2019, p. 1309175, doi:10.1155/2019/1309175

[33] Farghali, Hassan, *et al*. "SIRT1 Modulators in Experimentally Induced Liver Injury." Oxidative Medicine and Cellular Longevity, vol. 2019, 2019, p. 8765954, doi:10.1155/2019/8765954

[34] Shin, Myoung-Sook, *et al*. "A Hydroxypropyl Methylcellulose-Based Solid Dispersion of Curcumin with Enhanced Bioavailability and Its Hepatoprotective Activity." Biomolecules, vol. 9, no. 7, 2019, p. 281, doi:10.3390/biom9070281

[35] He, Xue, *et al*. "Protective Effect of Pyrrolidine Dithiocarbamate on Isoniazid/Rifampicin-induced Liver Injury in Rats." Molecular Medicine Reports, vol. 21, no. 1, 2020, pp. 463–469, doi:10.3892/mmr.2019.10817

[36] Menzies, Dick, *et al*. "Four Months of Rifampicin or Nine Months of Isoniazid for Latent Tuberculosis in Adults." The New England Journal of Medicine, vol. 379, no. 5, 2018, pp. 440–453, doi:10.1056/nejmoa1714283

[37] An, Zhuoling, *et al*. "Metabolomics of Hydrazine-Induced Hepatotoxicity in Rats for Discovering Potential Biomarkers." Disease Markers, vol. 2018, 2018, pp. 1–12, doi:10.1155/2018/8473161

[38] Darvin, S. Sylvester, *et al*. "Hepatoprotective Effect of Lawsone on Rifampicin-Isoniazid Induced Hepatotoxicity in in Vitro and in Vivo Models." Environmental Toxicology and Pharmacology, vol. 61, 2018, pp. 87–94, doi:10.1016/j.etap.2018.05.006

[39] Ramappa, Vidyasagar, and Guruprasad P. Aithal. "Hepatotoxicity Related to Anti-Tuberculosis Drugs: Mechanisms and Management." Journal of Clinical and Experimental Hepatology, vol. 3, no. 1, 2013, pp. 37–49, doi:10.1016/j.jceh.2012.12.001

[40] G. V. Zodape, P. P. Bhise. Effect Of *Aloe Vera* Extract And Isoniazid – Rifampicin Drug On Liver Histological

Studies Of Male Wistar Rats. international Journal of Pharmaceutical Sciences and Research. Vol. 9, no. 10, pp. 4318-4325, doi: 10.13040/IJPSR.0975-8232

[41] Sankar, M., *et al.* "Hepatoprotective Activity of Heptoplus on Isoniazid and Rifampicin Induced Liver Damage in Rats." Indian Journal of Pharmaceutical Sciences, vol. 77, no. 5, 2015, pp. 556–562, doi:10.4103/0250-474x.169028

[42] Sabiu S, Wudil AM, Sunmonu TO. Combined Administration of *Telfairia occidentalis* and *Vernonia amygdalina* Leaf Powders Ameliorates Garlic-induced Hepatotoxicity in Wistar Rats. Pharmacologia ,Volume 5, Issue 5, 2014, pp. 191–8

[43] Wagay, Nasir Aziz, *et al*. "Secondary Metabolite Profiling, Anti-Inflammatory and Hepatoprotective Activity of *Neptunia Triquetra (Vahl) Benth*." Molecules (Basel, Switzerland), vol. 26, no. 23, 2021, p. 7353, doi:10.3390/molecules26237353

[44] Moharram, Fatma Abd-Elkader, *et al*. "Phenolic Profile, Anti-Inflammatory, Antinociceptive, Anti-Ulcerogenic and Hepatoprotective Activities of *Pimenta Racemosa Leaves*." BMC Complementary and Alternative Medicine, vol. 18, no. 1, 2018, doi:10.1186/s12906-018-2260-3

[45] Zhou, Heng, *et al*. "Enhanced Regeneration and Hepatoprotective Effects of Interleukin 22 Fusion Protein on a Predamaged Liver Undergoing Partial Hepatectomy." Journal of Immunology Research, vol. 2018, 2018, p. 5241526, doi:10.1155/2018/5241526

[46] Junejo, Julfikar Ali, *et al*. "Exploration of Antioxidant, Antidiabetic and Hepatoprotective Activity of *Diplazium Esculentum* - A Wild Edible Plant from North Eastern India." Future Journal of Pharmaceutical Sciences, vol. 4, no. 1, 2018, pp. 93–101, doi:10.1016/j.fjps.2017.10.005

[47] González, Liliana Torres, *et al*. "In Vitro Assessment of Hepatoprotective Agents against Damage Induced by Acetaminophen and CCl4." BMC Complementary and Alternative Medicine, vol. 17, no. 1, 2017, p. 39, doi:10.1186/s12906-016-1506-1

[48] Urfi, Mirza Kalam, *et al*. "The Role of *Tamarix Gallica* Leaves Extract in Liver Injury Induced by Rifampicin plus Isoniazid in Sprague Dawley Rats." Journal of Dietary Supplements, vol. 15, no. 1, 2018, pp. 24–33, doi:10.1080/19390211.2017.1310783

[49] Doß, Sandra, *et al*. "Hepatotoxicity of Antimycotics Used for Invasive Fungal Infections: In Vitro Results." BioMed Research International, vol. 2017, 2017, pp. 1–10, doi:10.1155/2017/9658018

[50] Li, Deng-Ke, *et al*. "Hepatotoxicity in Rats Induced by Aqueous Extract of *Polygoni Multiflori Radix*, Root of *Polygonum Multiflorum* Related to the Activity Inhibition of CYP1A2 or

CYP2E1." Evidence-Based Complementary and Alternative Medicine: ECAM, vol. 2017, 2017, p. 9456785, doi:10.1155/2017/9456785