ISSN: 0975-3583, 0976-2833 VOL12, ISSUE 10, 2021

ASSESSMENT OF HEPATOPROTECTIVE PROPERTY OF SELECTED PLANTS IN PARACETAMOL-INDUCED HEPATOTOXICITY

[1]Dr. V. Padmaja, [2]Dr. G. Sruthi,[3]Mr. P. Aravind

[1]Professor, [23]Assistant Professor

[1]Department of pharmacognosy

[2]Department of pharmacy practice

[3]Department of Pharmacology

Vaagdevi Institute of Pharmaceutical Sciences, Bollikunta, Warangal. Telangana.

ABSTRACT

The primary organ responsible for the body's energy generation and nutrition metabolism is the liver. It is also required for the kidneys to metabolize and eliminate toxic chemicals and exogenous medications. A multitude of environmental contaminants, pathogenic microorganisms, viruses, medications, and chemical agents may all induce hepatotoxicity, which can lead to a range of hepatic disorders, including cirrhosis, fibrosis, hepatitis, jaundice, and necrosis. Ayurveda is an age-old Indian medical system that has been used consistently to treat a wide range of illnesses in people from ancient times. Medicinal plants are an important source of medicinal chemicals that are utilized to create medications that effectively treat a range of human disorders, including diseases of the liver. As a result, the pharmaceutical industry is starting to use medicinal plants to create safe and efficient medications for the treatment of newly discovered human ailments. Thus, the goal of this study is to gather information on medicinal plants that have been shown to be hepatoprotective when it comes to hepatotoxicity caused by drugs.

Key words: alcohol, carbon tetrachloride, paracetamol, hepatotoxicity, and hepatoprotection; medicinal plants..

I. INTRODUCTION

Liver is the principal and metabolic organ involved in the metabolism of vital molecules. Besides the metabolic role, it plays a central role in detoxification and excretion of endogenous and exogenous compounds thereby protecting body from the harmful substances.1 In this process, the liver injury occurs due to prolonged exposure with xenobiotics and their metabolites.2 Liver is also involved with almost all the biochemical pathways of growth, fight against diseases, nutrient supply and energy metabolism. Liver stands out from rest of the organs due to its regenerative property in response to liver damage.3 Apart from the drugs (paracetamol, antibiotic, antituberculosis and chemotherapeutic drugs), there are various other chemicals account for liver injury including alcohol consumption, heavy metals used in industries like lead, arsenic etc (Figure 1).4,5 Chemical induced hepatotoxicity has been extensively studied in animal model and the changes in biochemical pathways in association with pathological progress in the liver have been well documented.6,7 Hepatic damage results in necrosis, jaundice, fibrosis, cirrhosis, hepatitis, liver carcinoma etc.8 Liver diseases are one of the leading causes of illness and death globally. According to WHO estimates about 1.4 million deaths worldwide are due to the liver diseases. Although, modern medicine may treat to hepatic

ISSN: 0975-3583, 0976-2833 VOL12, ISSUE 10, 2021

diseases, but they also cause numerous side effects in the human body.9

In the Ayurvedic system of Indian medicine, people used medicinal plants for centuries to manage the primary health care need. Plant-based therapy still rely for the prevention and treatment of health related problems for thousands years including liver diseases.10 Conventional medicine is now pursuing the use of natural products such as herbs to provide the support that the liver needs on a daily basis.11 Therefore, it is essential to explore the suitable herbal drugs that could replace the chemical ones.

Figure 1: Possible risk factor for development of liver diseases.

Indian medicinal plants also provide a rich source for antioxidants that are known to prevent different diseased states. The antioxidant protection is observed at different levels. The medicinal plants also contain other beneficial compounds like phytochemical ingredients for functional foods. Hence, the global knowledge about Ayurveda and Indian herbals will hopefully be enhanced by information on the evidence-base of these plants. This will yield rich dividends in the coming years. Plants with medicinal properties are considered as more reliable and efficient options and also reported to be used traditionally to treat liver ailments. Many traditional plants are being used traditionally to cure various ailments in rural and tribal villages in India.12 Majorly plant-based preparations have been used to treat liver disorders. Herbal compounds perform natural process of healing in the human body. There has been a shift in universal trend from synthetic to herbal medicines for the prevention of diseases and ailments. The World Health Organization [WHO] estimates that 4 billion people use herbal medicines for some aspect of primary healthcare.13,14 A large experimental work is now being done on ethnopharmacology of herbal medicines. Search of new herbal drugs with better potential of healing and high safety profile is the current area of research interest. Numerous medicinal plants and their bioactive compounds have been studied and found to have hepatoprotective property against various types of drug-induced hepatotoxicity (Table 1, 2) and this review mainly summarized the drug-induced hepatotoxicity and hepatoprotective medicinal plants which have been evaluated in vivo and in vitro model.

II. MODEL HEPATOTOXICANTS

Acetaminophen (Paracetamol)

Acetaminophen also known as paracetamol or N-acetylp- aminophenol [APAP]. A safe and effective analgesic and antipyretic drug under recommended.15,16 Recommended dosage of APAP ranges 325-650 mg every 4-6 hr in adults with a maximum of 4g a day and 10-15 mg/kg every 4-6 hr with maximum of 50-75 mg/kg in children.17,18 Under therapeutic dosage, APAP is generally metabolized in the liver (5-9%) by Cytochrome P-450 enzyme system into the reactive metabolite called N-acetyl-p-benzo-quinoneimine (NAPQI) but majority 80-90% was metabolised via phase II metabolic pathway (glucuronidation and sulfation) in which APAPreduced glutathione (GSH]) conjugate is catalyzed by UDP-glucuronosyl transferases (UGT) and sulfotransferase (SULT), into non-toxic compounds: glucouronidated and sulfated metabolites which are eliminated through urine (Figure 2). Although, APAP's consumption for longer days may potentially harmful to the liver.19 Because NAPQI metabolite is produced

ISSN: 0975-3583, 0976-2833 VOL12, ISSUE 10, 2021

in excess amount which caused lipid peroxidation and it may bind to cellular proteins forming protein adducts resulting in depletion of metabolic energy (adenosine triphosphate, ATP) and cell necrosis.20 The APAP hepatotoxicity is the classical example of direct liver injury which can cause acute and severe liver injury in both human and experimental animals.21

APAP hepatotoxicity is currently the single most important cause for acute liver failure worldwide and is associated with significant number of deaths.22 Metabolic toxicity of APAP has been well studied in humans and experimental animals.23 More than 50% of all cases of acute liver failure in the United States from 1997 to 2002 have been shown to result from exposure to drugs and 40% of these have been attributed to acetaminophen ingestion.24 It has been studied that hepatotoxicity occurs following ingestion of a single dose of APAP only when a dose >125 mg/kg [7.5 g in a 60 kg individual] is absorbed and the likelihood of toxicity increased substantially as the absorbed dose exceeds 250 mg/kg and LD50 of APAP 3.7 g/kg in male rats.24,25

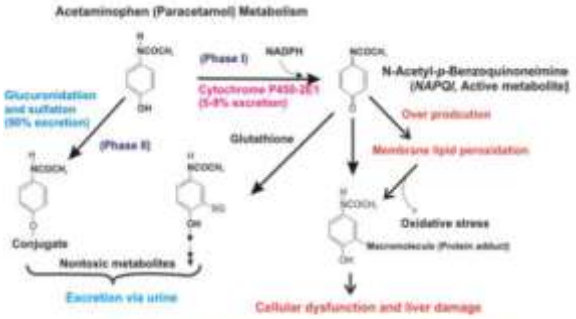
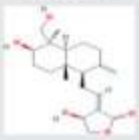
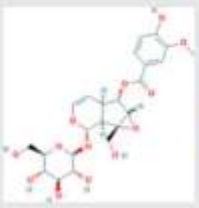


Figure 2: Metabolism of Acetaminophen with the hepatotoxicity.

Table 1: List of few hepatoprotective medicinal plants against toxic chemical induced liver damage in experimental animals.

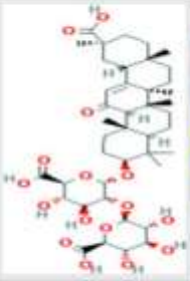
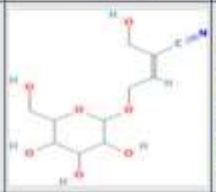
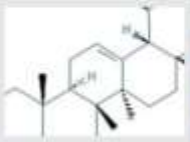
Medicinal Plants	Part used	Hepatotoxicants	Biochemical Parameters studied for hepatoprotection
Sida acuta[17]	Root	APAP	Hexobarbitone, in vitro LPO and histopathology
Sphaeranthus indicus[18]	Flower head	APAP	AST, ALT, ACP, SALP, bilirubin, protein, LPO, SOD, CAT and GPX, Histology
Clausena dentata[19]	Stem bark	APAP	AST, ALT, ALP, total bilirubin, GGTP and protein
Cassia fistula[20]	Root	CCl_4	SGOT, SGPT, ALP and Total protein and histopathology
Kyllingaperviridis[21]	Rhizomes	CCl_4	ALT, AST, SALP, total bilirubin and histopathology
Zanthoxylumarmatum DC[22]	Bark	CCl_4	ALT, AST, SALP, bilirubin total protein albumin, GSH and LPO, Histopathology
Trichosanthes cucumerina[23]	Whole plant	CCl_4	ALT, AST, SALP, bilirubin total protein albumin, GSH and LPO, Histopathology
Cichorium glandulosum[24]	Root	CCl_4	AST, ALT, SALP, DPPH inhibition and LPO
Carissa carandas Linn.[25]	Root	CCl_4 and APAP	ALT, AST, SALP, bilirubin total protein Uric acid, GSH, LPO, SOD, CAT and histopathology
Cassia occidentalis[26]	Leaf	APAP and Alcohol	ALT, AST, SALP, bilirubin, albumin, serum cholesterol, serum total lipids and histopathology
Vitis vinifera[27]	Leaf	Alcohol	AST, ALT, SALP, LDH, GGT, bilirubin, urea, creatinine, histopathological studies
Azadirachta indica[28]	Leaf	Alcohol	AST, ALT, ALP, protein, albumin, GSH, SOD and CAT
Emblica officinalis[29]	Fruit	Alcohol	AST, ALT, LPO, SOD, CAT, GST, SALP and histology

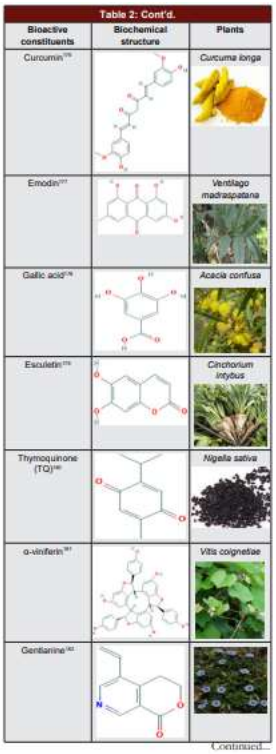
Table 2: Bioactive plant constituents with hepatoprotective potential.

Bioactive constituents	Biochemical structure	Plants
Andrographolide[170]		*Andrographis paniculata* 
Silybin[171]		*Silybum marianum* 
Picroside II[172]		*Picrorhiza kurroa* 

ISSN: 0975-3583, 0976-2833 VOL12, ISSUE 10, 2021

Table 2: Cont'd.

Bioactive constituents	Biochemical structure	Plants
Glycyrrhizin[173]		*Glycyrrhiza glabra* 
Sarmentosin[174]		*Sedum* 
Ursolic acid[175]		*Clerodendrum* 



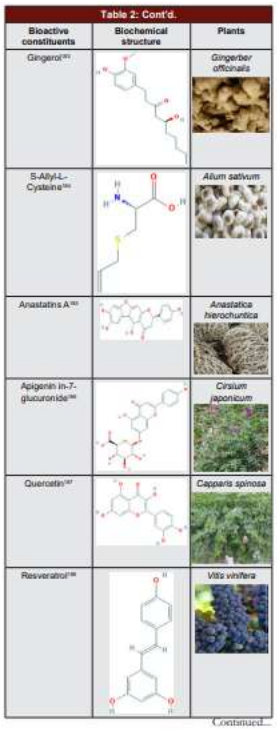
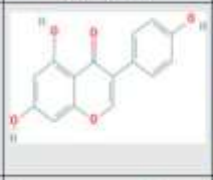
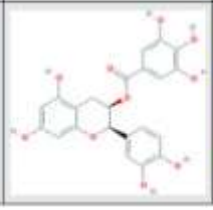


Table 2: Cont'd.

Bioactive constituents	Biochemical structure	Plants
Genistein[189]		*Glycine max* 
Epicatechins gallate[190]		*Camelia sinensis* 

Several investigators suggested that APAP toxicity was associated with increased level of hepatocellular enzymes viz., AST, ALT, LDH and SALP into circulation.26 It is well documented that the antioxidant enzymes (SOD, CAT, GPx, GR, G-6-PDH and GST) were decreased by APAP induced liver toxicity.27,28 Marked increased in serum globulin, bilirubin and total protein with significant decreased the albumin level after paracetamol administration were seen.29 Some studies have implicated a role for mitochondrial damage in the toxic process initiated by APAP in hepatocytes.30 Inhibition of cellular respiration due to impairment of mitochondrial function, DNA damage, decreased activity of Na+-K+ - ATPase were found in hepatocytes after paracetamol exposer.31,32 In vivo studies showed that APAP exposure induces DNA single-strand breaks in mice and rats, aneuploidy in rat embryo cells.33

Carbon tetrachloride (CCl4)

Carbon tetrachloride (CCl4) is a chlorinated organic solvent and its overexposure maytoxic to many organs. It is a colorless and highly volatile liquid with a sweetish [ethereal] odor. Upon heating, it breakdowns to highly toxic fumes of phosgene. It is primarily utilized for production of chlorofluorocarbons that are used as refrigerants. It has also been served as an antihelminthic, insecticide dispersant, dry-cleaning agent, grain-fumigant and fire extinguisher.34 Carbon tetrachloride can be

ISSN: 0975-3583, 0976-2833 VOL12, ISSUE 10, 2021

absorbed via oral (mouth) and inhalation (lungs) routes and dermal (skin) route both in humans and animals. It is a well-known hepatic toxin used to induce liver damage in laboratory animals like mice and rat to evaluate hepatoprotective effect of medicinal plants. It is metabolized in the liver by an nicotinamide adenine dinucleotide phosphate [NADPH]-dependent CYP450- 2E1 enzyme, forming free radicals, trichloromethyl (• CCl3) radical and with further oxidation to trichloromethyl peroxy (• O–O–CCl3).35,36 These free radicals attack on fatty acids in cell membranes and induce lipid peroxidation which cause further another reactive aldehydes (e.g., formaldehyde and acetaldehyde etc.). The aldehydes react with reduced glutathione [e.g., GSH], and reduces the GSH level in liver cells. GSH is an intracellular antioxidant which protects cells against free radical damage.37 Over production of free radicals by CCl4 metabolism may also induce DNA damage which contribute to the genotoxicity of CCl4 . Lipid peroxidation also causes cell membrane disruption thereby hepatic enzymes such as Aspartate transaminase [AST] and alanine transaminase [ALT] and bilirubin content released into the blood stream.38 This in turn activates protein degradation inflammation and cell necrosis which can also contribute to cytotoxicity (Figure 3).39

CCl4 metabolites cause alteration in Ca2+sequestration, lipid homeostasis and cytokines release and loss of energy metabolism.40 The metabolism of CCl4 has been investigated in the rat, rabbit, dog and human.41 Many investigators have utilized CCl4 to induce liver cirrhosis in experimental animals.42-44 Administration of CCl4 caused liver damage that mimics natural causes. It medicates changes in liver functions that ultimately lead to destruction of hepatocellular membrane. Peroxidation of lipids, covalent binding to macromolecules, disruption of metabolic mechanism in mitochondria, decrease levels of phospholipids, increase triglyceride levels, inhibition of calcium pump of microsomes and decreased activities of antioxidant enzymes Superoxide dismutase (SOD), Catalase, Glutathione peroxidase (GPx), Glutathione Reductase (GR) which may cause liver necrosis.45-47

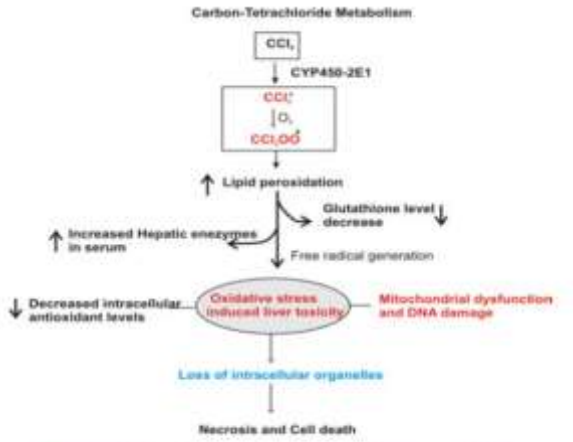


Figure 3: Metabolism of CCl_4 with the hepatotoxicity.

Alcohol (Ethanol)

Alcohol addiction is a major public health burden and estimated to cause about 20–30% of liver cirrhosis. It also increased motor vehicle accidents worldwide. It is estimated that 15 to 30% of chronic heavy drinkers eventually develop severe liver diseases. Alcoholic fatty liver may progress to alcoholic hepatitis and finally to cirrhosis and liver failure.60 In the India, chronic alcohol abuse is the leading cause of liver cirrhosis. Alcohol, the most commonly consumed xenobiotic, generates ROS species whether it is used over a long period of time. ALD ranges from reversible fatty liver (steatosis), to more severe alcoholic hepatitis and fibrosis and cirrhosis and end stage liver disease. Also obesity with prolonged alcohol intake increase the risk of irreversible liver damage.61 People who consume or addicted alcoholic have the major risk to develop alcoholic liver disease (ALD) such as hepatitis and cirrhosis.62,63 ALD pathway includes elevation of NADH/NAD+ ratio, causing lipid accumulation and up-regulation of cytochrome

ISSN: 0975-3583, 0976-2833 VOL12, ISSUE 10, 2021

P4502E1 (CYP2E1), resulting in oxidative stress and cellular inflammatory.64

Habitual consumption of Alcohol is one of the most common causes of liver disease in the world.65 There is increasing evidence that the prenatal environment can influence the risk of developing some chronic diseases in the offspring's later in life.66,67 Alcohol-related disorders are one of the challenging current health problems with far reaching medical, social and economic consequences. Long-term alcohol use potentially results in serious illnesses, including fatty liver, diabetes, hyper triglyceridaemia, cirrhosis and cardiovascular disease and dementia.68

In the hepatocyte, there are three systems that metabolizes ethanol located in three different cellular compartments: alcohol dehydrogenase located in the cytosol, the microsomal ethanol oxidizing system situated in the ER and catalase located in the peroxisomes.69 Alcohol is mainly metabolised in the liver. Normally about 10 gm of ethanol is metabolised in one hour. Phase I metabolism is involved in the induction of alcohol metabolism enzymes, especially in the gastrointestinal tract where it is converted to the acetaldehyde. Acetaldehyde is known to produce toxic effects on the liver cells and retard the rate of phase II metabolism. Accumulation of acetaldehyde leads to the formation of protein adducts, resulting in metabolic disturbances (Figure 4).70

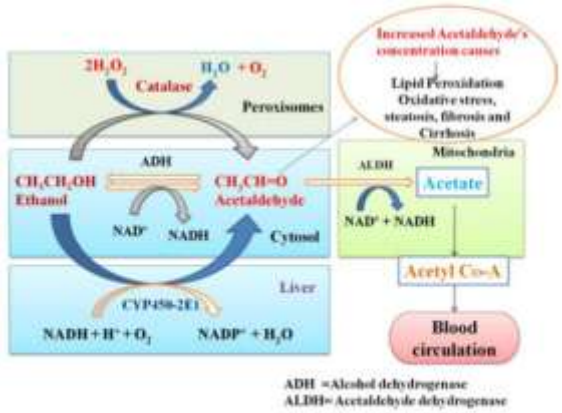


Figure 4: Oxidative pathway of Alcohol Metabolism with the hepatotoxicity.

Non-Alcoholic fatty liver disease

It is modern liver disease usually seen in obese or overweight people and children. Non-alcoholic fatty liver disease (NAFLD) refers wide a range of clinical conditions due to over accumulation of fat in the liver.81 In India, obesity is rising health problem particularly in urban areas which is more public health concerns including malnutrition. Overweight or obesity is reported about 30-65% of urban population of India. High-Fat Diet (HFD), unhealthy foods, physical inactivity and genetic factors. HFD is thought to be one of the main key factors for development of obesity. HFD is also main causative agent for nonalcoholic fatty liver diseases (NAFLD) leading to significant burden of morbidity and mortality in world population.82 Some diabetic patients may have insulin resistance due to obesity. In India, the rate of hepatic diseases including fatty liver in obese people has been reported to be much higher about 8-30%.83 It is a chronic liver disease that affects a high proportion of the world's population and represents a major cause of liver-related morbidity and mortality. Fatty liver is characterized by accumulation of fats (Triglycerides) in the liver resulting in oxidative stress, steatosis, fibrosis and cirrhosis.84,85

ISSN: 0975-3583, 0976-2833 VOL12, ISSUE 10, 2021

Antituberculosis drugs

Tuberculosis (TB) is a serious infectious disease which can be fatal if not treated in time. TB is completely curable with regular and on time treatment with anti-Tuberculosis drugs like Isoniazid (INH), Rifampicin (RMP) and pyrazinamide (PZA).86 However, these anti-TB drugs are associated with drug-Induced Liver Injuries (DILI) and thus have their own drawbacks and ill effects on health system. N-acetyl transferase metabolize Isoniazid (INZ) to acetyl-isoniazid which in turn form acetyl hydrazine and reactive acetyl species. Rifampicin (RMP) increases the rate of reactive acetyl species formation. These reactive acetyl species cause oxidative stress leading to hepatotoxicity.87 Liver enzyme elevation is an indicator of Anti-TB DILI which ranges from 5-30%. Extreme effects of Anti-TB treatment are liver injury, neurological disfunctioning and gastrointestinal ailment etc.88

Medicinal Plants with Significant Hepatoprotective Activity Andrographis paniculata (Family: Acanthaceae)

Andrographolide, the active constituent isolated from the Andrographis paniculata's leaf and aerial part, which showed a significant hepatoprotectiv activity against APAP induced toxicity on ex-vivo preparation of isolated rat hepatocytes.89 Today, it is involved in about 26 different Ayurvedic formulations used to treat liver disorders such as jaundice and hepatitis. Andrographolide was reported to improve gall bladder function, increases bile flow and has been found to be as effective as silymarin in protecting the liver. It also has showed anti-diabetic effect in streptozocin-induced hyperglycaemic rats and diabetic nephropathy. It maintains the liver function enzymes (AST, ALT and LDH) by reducing the lipid peroxidation as well as regulate the level of glutathione and antioxidant enzymes (Superoxide dismutase, Catalase, Glutathion peroxidase and Glutathione reductase) in carbon tetrachloride induced toxicity.90

Boerhaavia diffusa (Family: Nyctaginaceae)

It is known as Punarnava. The roots of Boerhavia diffusa are known tradionally for liver cure and used for the treatment of various liver problems due to their safety and efficacy. The root contain various types of flavonoids, isoflavonoids, glycoproteins and steroids which make it potent free radical scavenger.91 The root extract hasb been reported to have potent antiviral efficacy of against hepatitis B and C viruses.92 Its extract also increases normal bile flow and antioxidant defence system with improving cellular morphology in heptotoxicity in rats suggesting its strong hepatoprotective activity.93

Eclipta alba (Family: Asteraceae)

In ayurvedic medicine, its leaf extract is considered a powerful liver tonic and rejuvenative. It also has traditional external uses, like athlete foot, eczema and dermatitis. The alcoholic extract of Eclipta alba exhibited antihepatotoxic effect in carbon tetrachloride and galactosamine induced acute liver damage. It showed significantly stimulatory effect on hepatocyte cell regenration. regulates the levels of hepatic serum enzymes (AST and ALT) hepatic microsomal drug metabolizing enzymes and restores the normal architecture of liver cells against toxicity.94 It has been reported that phytochemiclas wedelolactone and demethylwedelolactone may possible components behind the hepatoprotective effect against liver disorders.95

Silybum marianum (Family: Asteraceae)

A well-known Hepatoprotective plant and it is a flavonolignan derived from the seeds of Silybum marianum called as milk thistle. It has good hepatoprotection in various hepatotoxic models of experimental liver disease in laboratory animals.152 It has been clinical tested hepatoprotective drug and used for the alcoholic fatty liver, jaundice, viral hepatitis and drug-

ISSN: 0975-3583, 0976-2833 VOL12, ISSUE 10, 2021

induced liver diseases. Hepatoprotective activity of silymarin has been reported in acute and chronic liver disease by various researchers across the world against carbon tetrachloride, alcohol, paracetamol, galactosamine and thioacetamide toxicity.153 Scientific and clinical studies on Silibinin confirmed that it has in vivo, in vitro and in silico potential hepatoprotective, anti-inflammatory and immune-modulating effects. It has anti-inhibitory effect on hepatitis C virus (HCV), NS5B polymerase and antioxidative stress, antifibrosis and anticancer activities.154 Animal studies suggested that silymarin flavoliganans increases hepatic glutathione and antioxidant enzymes levels generation in hepatocytes. It helps in drug detoxification and also acts positive modulatior for liver regeneration against liver diseases. Silybin blocks the regulatory molecules such as CDK2, CDK4, cyclin E and cyclin D1 proteins in the cell division of cancer cells.155

Silymarin is standard drug used to compare the hepatoprotective activity of the other plant extract. Its mechanism of action includes inhibition of hepatotoxin binding to receptor sites on the hepatocyte membrane, reduction of glutathione oxidation to enhance its level in the liver and intestine, antioxidant activity and stimulation of ribosomal RNA polymerase and subsequent protein synthesis leading to enhanced hepatocyte regeneration. Silymarin may make a breakthrough as a new approach to protect other organs in addition to liver. The most remarkable use of silymarin is in the treatment of mushroom poisoning, hepatitis, alcoholic liver disease and cirrhosis, psoriasis and hypercholesterolemia.156

III. CONCLUSION

The many pharmacological characteristics of medicinal plants that have been the subject of experimental research were gathered in this work. It is important to ascertain and describe the primary chemical extracted from the plants that may have hepatoprotective properties. Medicinal herbs may have hepatoprotective properties due to their ability to reduce oxidative stress and modify the metabolic pathways that cause hepatotoxicity. Medicinal plants high in phytochemicals are an excellent source of antioxidant activity, which is crucial in the fight against hepatic harm.

These findings might serve as justification for more research on the comprehensive pharmacological assessment of hepatoprotective medicinal plants.

REFERENCES

1. Su LJ, Ding GW, Yang ZL, Zhang SB, Yang YX, Xu CS. Expression patternsand action analysis of genes associated with hepatitis virus infection during rat liver regeneration. World J Gastroenterol. 2006;12(47):7626-34.
2. Lu Y, Hu D, Ma S, Zhao X, Wang S, Wei G, et al. Protective effect of wedelolactone against CCl4 -induced acute liver injury in mice. Int Immunopharmacol. 2016;34:44-52.
3. Woolbright BL, Jaeschke H. The impact of sterile inflammation inacute liver injury. J Clin Transl Res. 2017;3(1):170-88.
4. Masuda Y. Learning toxicology from carbon tetrachloride-induced hepatotoxicity. J Pharm Soc Jpn. 2006;126(10):885-99.
5. Singh D, Cho WC, Upadhyay G. Drug-Induced Liver Toxicity and Prevention by Herbal Antioxidants: An Overview. Fron Physiol. 2016;6:363.
6. Adewale OB, Adekeye AO, Akintayo CO, Onikanni A, Saheed S. Carbon tetrachloride (CCl4)-induced hepatic damage in experimental Sprague Dawley rats: Antioxidant potential of Xylopia aethiopica. Int J Pharmacol. 2014;3(2):118-23.
7. Zuzana P, Marie H, Helena D, Eva S, Alena L, Lenka B, et al. Silymarin

ISSN: 0975-3583, 0976-2833 VOL12, ISSUE 10, 2021

prevents acetaminophen-induced hepatotoxicity in mice. PLoS One. 2018;13(1):e0191353.

8. Wang X, Wu Q, Liu A, Anadón A, Rodríguez J. Martínez-Larrañaga M, et al. Paracetamol: Overdose-induced oxidative stress toxicity, metabolism and protective effects of various compounds in vivo and in vitro. Drug Metab Rev. 2017;49(4):395-437.
9. Yang J, Li Y, Wang F, Wu C. Hepatoprotective effects of apple polyphenols on CCl4 -induced acute liver damage in mice. J Agric Food Chem. 2010;58(10):6525-31.
10. Fallah HH, Alavian SM, Heshmat R, Heydari MR, Abolmaali K. The efficacy of Liv- 52 on liver cirrhotic patients: A randomized, double-blind, placebocontrolled first approach. Phytomedicine. 2005;12(9):619-24.
11. Murugaian P, Ramamurthy V, Karmegam N. Hepatoprotective Activity of Wedelia calendulacea L. against Acute Hepatotoxicity in Rats. Res J Agri Biol Sci. 2008;4(6):685-7.
12. Shakya AK. Medicinal plants: Future source of new drugs. I Journal of Herbal Med. 2016;4(4):59-64.
13. Jain S, Mohan R, Rai R. Ocimum sanctum as an Herbal Medicine: A Review. Int J Oral Maxillofac Implants. 2015;1:1-12.
14. Jose JK, Kuttan R. Hepatoprotective activity of Emblica officinalis and Chyavanaprash. J Ethnopharmacol. 2000;72(1-2):135-40.
15. Bunchorntavakul C, Reddy KR. Acetaminophen-related hepatotoxicity. Clin Liver Dis. 2013;17(4):587-607.