Pharmacogn. Rev.
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REVIEW ARTICLE

A Review on Some Medicinal Plants with Hepatoprotective Effects

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ABSTRACT

Liver diseases have become a major global health challenge and may be triggered by several toxic chemicals, which include chemotherapeutic agents, thioacetamide, carbon tetrachloride, certain antibiotics, excessive alcohol consumption, and pathogenic microbes. Hence, safeguarding a healthy liver is vital for good health and well-being. Despite advances in pharmacology, the demerits associated with synthetic drugs have outshone the merits. Treatment of liver diseases based on modern medical principles is becoming ineffective and also associated with adverse effects of long-term use, in addition to prohibitive costs in developing countries. Thus, exploring medicinal plants which are easily available and cheap and do not involve strenuous pharmaceutical production processes appears to have gained worldwide attention as alternative therapeutic agents for the diseases. Consequently, emphasis has been placed on folkloric herbs with high efficacy, low toxicity, and cost-effectiveness. In this paper, literature search was conducted using various databases such as Google Scholar, ISI Web of Knowledge, and PubMed; we carried out a comprehensive review on existing information on some medicinal plants around the world with hepatoprotective prospects. Phytochemical compounds with hepatoprotective effects were also discussed, and finally, the future work in the field was also highlighted.

Key words: Bioactive compounds, hepatotoxicity, liver diseases, medicinal plant, pharmacology

INTRODUCTION

Liver is the most crucial and indispensable organ in the body with multifunctional capabilities. It is involved in the metabolism of nutrients such as lipids, proteins, and carbohydrates, as well as in the excretion of waste metabolites.[1] In addition, liver is also the first destination of toxins from the intestinal tract, and thus, it is involved in the breakdown and elimination of toxins such as drugs and other foreign chemical substances. The following are the specific functions of liver in the body.

It serves as a storage compartment for numerous substances such as glycogen, vitamins, minerals, and iron. Whenever there is depletion in the level of blood sugar in the body and energy is needed, the liver breaks down stored glycogen into glucose that is then utilized by the body.[2] It also detoxifies drugs, alcohol, chemicals, heavy metals, infectious organisms, as well as toxin by-products from the blood.[3] Furthermore, the liver removes blood contaminants and waste products such as chemicals, drugs, viruses, bacteria, parasites, fungi, pesticides and herbicides, fats, food additives, alcohol, and dead cells. In addition, the liver is usually known as the biochemical unit of the body since it carries out all functions through different organs such as the mouth, skin, and lungs. It metabolizes substances in the bloodstream before they are distributed to the different parts of the body where they are needed.[4] The liver performs its digestive role by producing bile, which is needed to digest and emulsify fats and oils as well as other substances, such as Vitamins A, D, E, and K. It also has the capability to synthesize some proteins such as blood proteins, enzymes, hormones, immune factors, and clotting factors. Finally, the liver has the ability to produce cholesterol, a carrier vessel that is capable of transporting energy-supplying fats needed for adenosine triphosphate generation in the body whenever there is depletion in the blood sugar level.

HEPATOTOXICITY AND LIVER DISEASES

Liver diseases are regarded as one of the leading global health issues prevalent in developing countries. These diseases are classified into different categories, namely hepatosis (noninflammatory), acute or chronic hepatitis (inflammatory), and cirrhosis or fibrosis (degenerative). The heavy metals, toxins, malnutrition, and over-the-counter drug use without doctors' prescription commonly cause them. Consequently, the aforementioned factors destroy and incapacitate the hepatocytes that finally result in hepatitis, jaundice, liver fibrosis, and alcoholic liver disease. The elevation of cholesterol in the bloodstream is one of the indicators of the liver injury/disease. High percentages of low-density lipoprotein cholesterol (LDL-C) and triacylglycerols (TAGs) are connected with a high risk of cardiovascular diseases.[5]

In addition, hepatic cell damage can also be caused by excessive alcohol consumption, toxic substances such as thioacetamide (TAA), abuse of certain drugs such as paracetamol (PCM), chemotherapeutic agents such as carbon tetrachloride ($CC1_4$), and also some organic and inorganic compounds, aflatoxin, microbes, and viral infections (for example,

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Access this article online

Quick Response Code:

Website: www.phcogrev.com

DOI: 10.4103/phrev.phrev_52_17

Cite this article as: Okaiyeto K, Nwodo UU, Mabinya LV, Okoh AI. A review on some medicinal plants with hepatoprotective effects. Phcog Rev 2018;12:186-99.

hepatitis A, B, C, and D), which have been thoroughly investigated.[6-8] The endoplasmic reticulum and mitochondrial cytochrome P-450 metabolize $CC1_4$ that subsequently generates reactive oxygen species (ROS, CCl_3O^-), which results in a chain reaction and perhaps triggers lipid peroxidation.

PCM is commonly used as a pain-relieving (analgesic) or fever-preventing (antipyretic) drug. The misuse of this drug at high dosage damages liver cells and consequently leads to liver cell injury or disease.[9] In addition, the excessive administration of PCM can lead to the death of most of the liver cells (necrosis) indicated by nuclear pyknosis and eosinophilic cytoplasm, which consequently lead to large excessive hepatic injury. When PCM is metabolized in the liver, it generates an oxidative product, N-acetyl-P-benzoquinoneimine that forms a covalent bond with the sulfhydryl groups of protein (cytochrome P-450 enzymes). This process consequently leads to glutathione (GSH) lipid peroxidative degradation which causes necrosis of hepatocytes.

TAA is another chemical substance that obstructs the free flow of RNA between the nucleus and cytoplasm that consequently leads to membrane damage. The TAA metabolite is accountable for this hepatic injury.[9] TAA has the ability to reduce hepatocytes as well as reduce the frequency of oxygen consumption. In addition, it reduces the volume of bile as well as its contents that are bile salts and deoxycholic acid. Hepatotoxin-associated liver injury makes excretion of bile defective that is manifested by an increase of serum levels in toxins.[10] Thus, maintaining the integrity of the liver at all times is imperative for human health.[11-13] Regardless of its extensive regenerative potential, constant exposure to environmental pollutants such as chemotherapeutic agents and xenobiotics could repress and suppress the normal protective ability of the liver, thereby leading to liver malfunctioning and consequently liver damage.[14]

On the other hand, the majority of the hepatotoxicity agents damage hepatocytes and subsequently impair the kidney function mostly through lipid peroxidation or other oxidative forms. In cases of liver damage, the capacity of the natural antioxidant system is inadequate. ROS are generated by environmental causes such as X-rays, pollutants, ultraviolet radiation, or metabolic process in the mitochondria.[15] The intracellular concentration of ROS solely depends on the rate at which they are generated by exogenous or endogenous factors as well as their elimination by several endogenous antioxidants such as enzymatic and nonenzymatic processes.[15]

Several reports have shown that oxidative stress triggered by free radicals is the main causative agent of liver damage such as degeneration, necrosis, swelling, and apoptosis of the hepatocytes. Liver injury or damage resulting from free radicals usually occurs via the mechanisms of lipid peroxidation and covalent binding with consequent tissue injury. ROS which include peroxyl, hydroxyl, alkoxy, and superoxide radicals destruct the membrane lipids, proteins, and nucleic acid, and this has also been linked to several aging-related issues together with atherosclerosis, diabetes mellitus, lung and kidney damage, liver disorders, cancer, inflammatory diseases, and cardiovascular diseases.[16,17] Lipid peroxidation interferes with cell membranes and consequently affects the structural integrity and functionality of the cell membrane that subsequently has a negative impact on the cell's potential to maintain constant ion gradients and transport.[18] On the other hand, liver damage can also be caused by drug abuse at high dosages and certain chemicals.[14] Table 1 and Figure 1 show some reported drugs with hepatotoxicity effects.

Table 1: Example of some drugs with hepatotoxicity effects

Drugs	Implication
Fluconazole	It leads to hepatitis; it increases the transaminase level, fulminant hepatic failure, and cholestasis
Amoxicillin	It moderates or brings about an increase in SGPT and SGOT levels, hepatic failure such as jaundice, acute cytolytic hepatitis, and hepatic cholestasis
Diclofenac	It elevates AST and ALT levels, jaundice, fulminant hepatitis, and liver necrosis
Rifampin	It leads to hepatitis, hyperbilirubinemia, and cholestasis
Ciprofloxacin	Elevation of SGOT alkaline phosphatase and SGPT levels occurs from cholestatic jaundice
Oral contraceptives	Benign neoplasm, hepatic vein occlusion, and jaundice, but rarely neoplasm of the liver
Chlorpromazine	It leads to infectious hepatitis with obstructive jaundice as a biomarker
Isoniazid	It elevates the serum transaminase level, severe and fatal hepatitis
Acetaminophen	It makes the cytochrome P-450-2E1 produce a toxic metabolite NAPQI that causes hepatic necrosis
Erythromycin	It increases SGPT and SGOT concentration, and it also brings about hepatocellular hepatitis that are sometimes associated with it

SGOT=Serum glutamic oxaloacetic transaminase, ALT=Serum alanine aminotransferase, AST=Aspartate aminotransferase, SGPT=Serum glutamic pyruvic transaminase, NAPQI=N-acetyl-P-benzoquinoneimine

FREE RADICALS AND LIPID PEROXIDATION

The free radical scavenging mechanism plays a major part in inhibiting the lipid peroxidation initiated by free radicals.[19] Ethanol metabolism increases lipid peroxidation and subsequently leads to hepatitis which later develops into cirrhosis.

Plant-based products that are less toxic have been used in recent times as hepatoprotective agents. Thus, continual exploration of plant diversities for novel hepatoprotective potential has been an area of active research in this field.[20] However, previous studies have documented that the overproduction of ROS reinforces oxidative stress, resulting in an injury mechanism associated with common clinical diseases, such as diabetes, kidney and liver injury, cancer, and heart disease;[21] maintaining the balance between ROS and antioxidant enzymes which include glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), and catalase (CAT) is important in preventing oxidative stress damage.[22]

The enzymatic antioxidant defense mechanisms entail Cu–Zn, Mn–SOD, CAT, and GSH reductase, which are natural lipid peroxidation protectors, and function by direct or sequential ROS removal, thus terminating or diminishing this process.[23] To avoid lipid peroxidation, it is essential to maintain the level of GSH, an important antioxidant in cytosol involved in the detoxification and excretion of xenobiotics.[24] Among xenobiotics, CCl_4 is considered a major causative agent of acute liver cell damage via free radical (trichloromethyl radical) generation.[25] Compounds that increase the activity of glutathione S-transferase which has the potential to convert toxic substances to harmless ones usually have an increasingly protective mechanism in the liver. Natural products including medicinal plants and their compounds have been reported to prevent and treat a lot of diseases due to their fewer side effects on the body systems.[26,27] The protective potentials of some herbal extracts on intoxicated liver have been documented by some researchers.[8,13,28]

ALCOHOL AND LIVER DISEASES

Currently, excessive alcohol consumption is one of the main causes of liver problems globally.[14] There is a connection between ethanol intake and alcoholic liver disease because alcohol metabolism takes place in the liver, and consequently, this process affects lipoprotein and lipid metabolism. Furthermore, alcohol dehydrogenase converts ethanol to acetate that generates ROS via cytochrome P4502E1.[29,30] The process that occurs in the liver results in oxidative stress [Figure 2] and subsequently

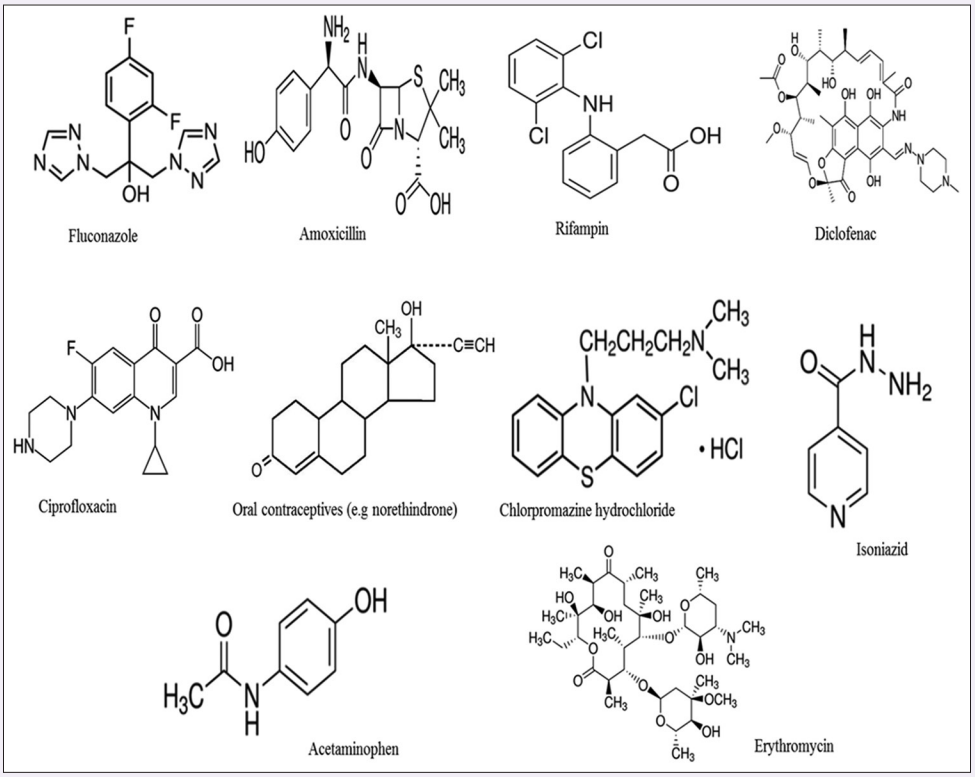

Figure 1: Chemical structure of some drugs with hepatoxicity effects

brings about hepatic damage and affects the structural rigidity of the hepatic cell membrane which allows the cytosolic enzymes to leak into the bloodstream. Consequently, the biochemical marker commonly used to determine liver damage is an increase in the cytosolic enzymes in the bloodstream.[31] Concentrations of aspartate transaminase (AST) and alanine transaminase (ALT) in the cytoplasm and mitochondria of damaged liver cells also increase. Leakage of the cell membrane causes an increase in serum hepatospecific enzymes due to the alteration of the liver cell membrane structure. In addition, high bilirubin concentration in the serum is a manifestation of an increase in the erythrocyte degeneration rate. Thus, the conservation of a healthy liver is imperative for human health.[32] Figure 2 shows the mechanism of alcohol-induced hepatotoxicity.

MEDICINAL PLANTS AS AN ALTERNATIVE TREATMENT

Liver damage is a metabolic disorder which is the most common cause of mortality and morbidity globally. Liver injury treatments have gained global attention in recent times because of many allopathic drugs and their toxic influence which leads to liver damage. Hence, folkloric herbs with hepatoprotective potentials to treat liver injury or disease have received considerable attention from researchers due mainly to their low toxicity and healing efficacy. Recently, several folkloric herbs have been investigated for their hepatoprotective role in experiments on animals. Traditional medicines have been utilized for the benefit of the beneficial outcomes of herbal medicine for human health. Varieties of molecules have been isolated and their physicochemical and pharmacological properties were studied. However, compounds and extracts need to be appropriately formulated to facilitate their physiological target and pharmacological activity. Factors such as low permeability and solubility could affect the absorption and delivery of bioactive molecules.[32] On the other hand, the shelf life of herbal medicines should be evaluated to monitor their stability during the period of use. Degradation reactions are enhanced by temperature, humidity, pH, oxygen, and light. Herbal medicines are complex mixtures of different classes of chemical compounds, such as carbohydrates, proteins, lipids, and secondary metabolites.[33]

Because of the negative effect allied with synthetic drugs, much effort has been made to identify novel sources of hepatoprotective agents.[34] In recent times, most of the hepatoprotective drugs available in the market for use against different kinds of liver diseases have plant-based origins, either as single-plant preparations or as poly-herbal mixtures. Folkloric herbs play an essential role in improving the quality of life of rural dwellers, especially in developing countries with inadequate modern health facilities.[1] Over 70,000 plant species have been used for therapeutic purposes. Although attention has been diverted to plants as natural treatment alternatives due to efficacy, the scientific rationale behind the plant preparation and dosage regimens has usually not well understood, and despite their efficacy and cost-effectiveness, the need to prioritize low-toxicity candidate plants becomes imperative, and although these herbal drugs are abundant in the market and the pharmacological ingredients have not been fully identified, some of the identified bioactive ingredients have been proved to have antiviral, antioxidant, anticarcinogenic, antifibrotic, and anti-inflammatory effects.[35,36]

IN VITRO AND *IN VIVO* HEPATOTOXICITY ASSAYS

The choice of appropriate treatment for the liver disease relies solely on the suitability of the model the system preferred for hepatic damage. Although a number of prototypes exist to assess the hepatoprotective prospect of any chemical or plant extract, most of these models have

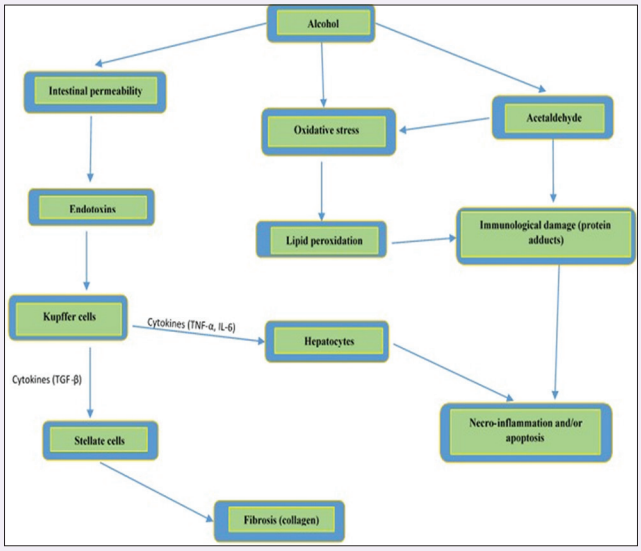

Figure 2: Mechanism of alcohol-induced hepatotoxicity[2]

limitations. Hence, it will be appropriate to combine these models for better results.[37] In a study carried out by Cerný *et al.*[38] *In vitro* assays such as hepatocyte cultures, perfused hepatocytes study with pathophysiological damage caused by various chemical substance (e.g., hypoxia hepatotoxins, or anoxia assays in perfused immobilized hepatocytes were documented. Some of the reported *in vivo* models are presented in Table 2. The majority of these studies on the hepatoprotective role of some medicinal plants are still based on the laboratory experiments.

Most organisms have their own antioxidant-based defense mechanisms which combat the activity of free radical species. The protective role of the endogenous antioxidant system in humans is not always adequate when the free radical species are much greater than the available antioxidant, and hence, additional antioxidants from different sources become important. Various antioxidant agents of plant origin appear to be effective in scavenging free radicals that lead to liver injuries.[39] Phytochemicals such as phenolics, thiols, and caretonoids present in herbal plants protect the human body against oxidative damage by ROS.[17] Therefore, attention is being diverted to promising medicinal plants that have the hepatoprotective potential to treat different kinds of liver disease. The folkloric herbs for treating all kinds of diseases have been in existence since ancient times due to their therapeutic efficacy and safety, and several herbs have been investigated for their hepatoprotective potential for the treatment of different types of liver disorders.[14] Numerous herbal formulations have proved to be effective therapeutic agents against various kinds of liver disorders [Table 2], and this review mainly focused on available literature on those that have been confirmed around the globe to have hepatoprotective properties.

SOME MEDICINAL PLANTS WITH HEPATOPROTECTIVE ACTIVITY

Dodonaea viscosa (*Sapindaceae*)

Dodonaea viscosa belongs to the soapberry family that is a species of flowering. *Sapindaceae* is widely distributed in the subtropical, warm, and tropical temperate regions of Africa, Americas, Australia, and Southern Asia.[47] This plant is locally referred to as "Sanatha" and is a local folkloric herb that has been utilized over centuries in the management of diabetes by traditional practitioners.[132] In a report by Ahmed *et al.*,[47] aqueous: methanolic (70:30) leaves extract of *D. viscosa* was found to display antihyperlipidemic and hepatoprotective activity in alloxan-induced diabetic rabbits. In this study, it was observed that serum levels of TAG, total cholesterol, LDL-C, HDL-CHL, ALT, and AST were reduced compared to experimental control sample. Furthermore, the extract meaningfully increased HDL-CHL, AST, and ALT levels. These findings show that the leaves extract of *D. viscosa* have hepatoprotective effect.

Phyllanthus muellarianus (*Euphorbiaceae*)

Phyllanthus muellarianus is a straggling, monoecious glabrous, or climbing shrub or small tree, which is commonly dispersed in Ivory Coast, Nigeria, Mali, Congo, Togo, South Africa, Senegal, and Uganda.[40] The extracts of various components of this plant have been used in the treatment of a diverse of ailments such as fever, paralysis, and bacterial infections.[133,134] Phytochemical screening of *P. muellarianus* leaves extract displayed the presence of phytochemical compounds such as furosin, isoquercetin, phaselic acid, corilagin, nitidine, geraniin, and gallic acid and might be accountable for its medicinal effect.[135,136] In 2017, Ajiboye *et al.* investigated the hepatoprotective capacity of aqueous extract of *P. muellarianus* leaf in hepatic damage induced by b-acetaminophen in Swiss albino mice with hepatocellular indices as the biomarkers, proinflammatory factors, oxidative stress, and lipid peroxidation.[40] Findings from this study showed that the aqueous leaf extract considerably ($P < 0.05$) attenuated acetaminophen-mediated alterations in the ALT, alkaline phosphatase (ALP), AST, albumin (ALB), and total bilirubin (TB). The antioxidant prospect of the aqueous leaf extract could be attributed to its ability to antagonize acetaminophen-mediated rise in these liver enzymes which indicates hepatoprotective effect against acetaminophen-mediated toxicity. Gallic acid, a well-known antioxidant agent which is one of the phytochemical compounds of this plant extract, was documented to reverse AST, ALT, and ALP and in acetaminophen-induced liver toxicity.[137]

Likewise, acetaminophen-mediated decrease in the activities of SOD, GSH, CAT, G6PH, and GSH-Px was significantly reduced in the liver of the rat. The rise in the level of conjugated dienes, malondialdehyde, lipid hydroperoxides, fragmented DNA, protein carbonyl, and tumor necrosis factor-alpha significantly decreased by aqueous leaf extract by the studied plant. It was further concluded that the plant demonstrated propitious prospect of being utilized as a dietary supplement food due to its prophylactic effect.[40]

Aquilaria agallocha (*Thymelaeaceae*)

This is a big tree growing up to 60–80 feet with thick a stem of 3–4 feet in diameter. It is native to Southeast Asia. The bark is papery thin and was sometimes used for writing just like Betula utilizing tree bark. Leaves are thin-like leather, shiny, and up to 3-inch long. Flowers are white and fruit is 1–2 inch long, smooth, and thin. The plant *Aquilaria agallocha* has several pharmacological effects and shows anticancer, antioxidant, anti-inflammatory, antidiabetic, analgesic, antihistaminic, antipyretic, laxative, antidiarrheal, antidiabetic, antihistaminic, anxiolytic, antimicrobial, sedative, antibacterial, ulcer, and anticonvulsant protective activities.[138] Alam *et al.*[72] proved the hepatoprotective role of ethanolic extract of *A. agallocha* (AAE) leaves (400 mg/ml) in PCM-induced hepatotoxicity in Sprague–Dawley (SD) rats. These results revealed that AAE leaves exert hepatoprotective effect as it exhibited protective effect contrary to PCM-induced hepatotoxicity in SD rats as shown by a substantial decrease in AST, ALP, ALT, LDH, CHL, and TB, increase in ALB and total protein concentration, and prevention of PCM-induced histopathological changes in the liver.[72]

Table 2: Medicinal plants with hepatoprotective potentials

Family	Name of the plant	Plant parts used	Extract used	Oral dose (mg/kg)	Hepatotoxicity inducing agents	Biochemical and histopathological parameter studied	Reference
Euphorbiaceae	*Phyllanthus muellarianus*	Leaves	Aqueous	400 mg/kg	Acetaminophen	ALP, ALT, AST, ALB, TB, CAT, SOD, GSH-Px, GSH	[40]
Scrophulariaceae	*Picrorhiza kurroa*	Roots rhizomes	Ethanol	2.60 ml/kg	CCl_4	SGOT, SGPT, ALP, CHL, TB, and TP	[41]
Fabaceae	*Bauhinia variegata*	Stem barks	Alcohol	100 and 200 mg/kg	CCl_4	AST, ALP, GGT, ALT, TBARS, and liver protein	[42]
Rubiaceae	*Galium aparine*	Whole plant	Alcohol	2 ml/kg	CCl_4	ALT, AST, and ALP	[43]
Cannaceae	*Canna indica*	Aerial parts	Methanol	100 and 200 mg/kg	CCl_4	SGPT, SGOT, TB, CAT, GSH, LPO	[44]
Moraceae	*Ficus cordata*	Roots	Methanol/ethyl acetate	400 mg/kg	CCl_4	LDH	[45]
Zingiberaceae	*Curcuma longa*	Rhizome	Ethanol	600 mg/kg	PCM	ALT, ALP, and AST	[46]
Sapindaceae	*Dodonaea viscosa*	Leaves	Methanol	500 mg/kg	Alloxan	AST, LDLC, ALT, HDL STG, and TC	[47]
Asteraceae	*Eclipta prostrata*	Fresh leaves	Methanol	10 80 mg/kg	CCl_4	ALT, AST, and serum bilirubin	[48]
Cyatheaceae	*Cyathea gigantea*	Leaves	Methanol	100 and 200 mg/kg	PCM	SGPT, SGOT, ALP, TB, TP	[49]
Araceae	*Alocasia macrorrhizos*	Leave and tuber	Ethanol and aqueous	200 mg/kg	CCl_4	Serum ALT and AST	[17]
Nyctaginaceae	*Boerhavia diffusa*	Roots	Ethanol	200 and 400 mg/kg	Country-made liquor	SGPT, SAP, TGs, and total lipid levels	[50]
Apocynaceae	*Leptadenia pyrotechnica*	Whole plant	Methanol, petroleum ether, chloroform, acetone, and aqueous	150 ml/kg	PCM	SGPT, TB, ALP, and SGOT	[7]
Asclepiadoideae	*Tylophora*	Leaves	Methanol	200 and 300 mg/kg	CCl_4	SGPT, ALP, SGOT, and bilirubin content	[51]
Arecaceae	*Phoenix dactylifera*	Fruit	Methanol	300 mg/kg	TAA	TBAST, ALT, and ALP	[52]
Asteraceae	*Tridax procumbens*	Aerial parts	Ethanol	300 mg/kg	d-GalN/LPS	AST, LDH, ALT, ALP, GGT, TB, and TBARS	[53]
Cactaceae	*Opuntia ficus-indica*	Leaves	Aqueous	2, mL/kg	CCl_4	AST, ALT, creatinine, urea, and uric acid	[54]
Rutaceae	*Clausena lansium*	Stem bark	Methanol	100 and 200 mg/Kg	CCl_4	Reduction in phenobarbitone, sleeping time and serum liver protein, serum AST, ALT, and ATP.	[55]
Apiaceae	*Apium graveolens*	Seeds	Methanol	250 mg/Kg	CCl_4	SGOT, SGPT, SALP, TP, TA, and GSH	[56]
Cactaceae	*Opuntia ficus-indica*	Stem	Aqueous	1500 mg/kg	CPF	ALAT, ASAT, ALP, LDH, CHL, and albumin	[57]
Rosaceae	*Agrimonia eupatoria*	Aerial part	Aqueous	100 and 300 mg/kg	Ethanol	AST and ALT	[58]
Vitaceae	*Vitis vinifera*	Leaves	Alcohol	125 mg/kg	CCl_4	AST and ALT	[59]
Polygonaceae	*Rheum palmatum*	Aerial part	N/A	25 and 100 mg/kg	CCl_4/ethanol	N/A	[60]
Pandanaceae	*Pandanus odorifer*	Roots	Ethanol	200 and 400 mg/kg	PCM	SGOT, SALP, SGPT, TB, and TGA	[61]
Rhamnaceae	*Ziziphus oenoplia*	Roots	Alcohol	150 and 300 mg/kg	INH and RIF	SGOT, SGPT, SALP, SB, SOD, CAT, GST, and GPx	[62]

Contd...

Table 2: Contd...

Family	Name of the plant	Plant parts used	Extract used	Oral dose (mg/kg)	Hepatotoxicity inducing agents	Biochemical and histopathological parameter studied	Reference
Asteraceae	*Cichorium intybus*	Leaves	Ethanol	50, and 100 mg/kg	CCl_4	ALT, AST, and ALP	[63]
Betulaceae	*Corylus avellana*	Leaves	Aqueous	NA	CCl_4 and acetaminophen	GPT and GOT	[64]
Lauraceae	*Cinnamomum cassia*	Bark	Ethanol	40 mg/kg	Dimethylnitrosamine	TP, albumin, TB, direct bilirubin, GOT, GPT, and ALP	[65]
Apiaceae	*Anethum graveolens*	Seeds	NA	500 and 1000 l/kg	CCl_4	SGPT, SGOT, and ALP	[66]
Anacardiaceae	*Pistacia lentiscus*	Gums	NA	NA	CCl_4	AST, ALT and MDA, GSH, GPx, GST, GR, SOD, and CAT	[67]
Lythraceae	*Punica granatum*	Edible portion (seed coats and juice)	Acetone	400mg/kg	INH and RIF	AST, ALT, and LDH	[68]
Rosaceae	*Rosa damascena* mill	Flower	Aqueous	250, 500 and 1000 mg/kg	Acetaminophen	AST, ALT, ALP, LDH, ALBTB, urea and creatinine, TBARS, and GSH	[69]
Cucurbitaceae	*Cucurbita maxima*	Aerial parts	Methanol	250 and 500 mg/kg	CCl_4	SGPT, SGOT, ALP, TP, and TB	[70]
Muntingiaceae	*Muntingia calabura*	Fruits	Methanol	50, 250, and 500 mg/kg	Acetaminophen	AST, ALT, and ALP	[71]
Thymelaeaceae	*Aquilaria malaccensis*	Leaves	Ethanol	400 mg/kg	PCM	AST, ALT, LDH, ALP, bilirubin, CHL, TP, and ALB	[72]
Berberidaceae	*Coptidis rhizoma*	NA	NA	120 mg/kg	CCl_4	ALT, AST, and SOD	[73]
Apiaceae	*Cynara scolymus L.*	Root	Hydroalcohol	900 mg/kg	CCl_4	ALT, ALP, AST, GSH, and CAT	[74]
Asteraceae	*Calendula officinalis*	Whole plant	Methanol	500 mg/kg	Acetaminophen/CCl_4	ALT, AST, and LDH	[75]
Asteraceae	*Taraxacum officinale*	Roots	Hydroalcoholic acid	250 mg/kg	Ethanol	TBARS, GST, GSH, SOD, CAT, GR, and GPx	[76]
Asteraceae	*Tragopogon porrifolius*	Edible root and shoot	Methanol	250 mg/kg	CCl_4	CAT, SOD and GSTAST, ALT, and LDH	[77]
Euphorbiaceae	*Baliospermum montanum*	Root	Methanol	2000 mg/kg	TAA	GOT, GPT, ALP, TB, TC, TB, and albumin	[78]
Fabaceae	*Tephrosia purpurea*	Aerial parts	Ethanol	500 mg/kg	TAA	AST, GSH, ALT, ALP, TB, GGT, and MDA	[79]
Euphorbiaceae	*Alchornea cordifolia*	leaves	Methanol	300 mg/kg	CCl_4	SGOT/AST, SGPT/ALT, ALP, and TB	[80]
Fabaceae	*Trigonella foenum-graecum* L.	Leaves	Ethanol	100 mg/kg	H_2O_2; CCl_4	ALT, AST, ALP, and GGT	[81]
Rutaceae	*Glycosmis pentaphylla* Corr.	Leaves, bark	Methanol	500 mg/kg	CCl_4	ALT/SGPT, AST/SGOT, CHL, bilirubin, and glucose	[82]
Acanthaceae	*Andrographis lineata* Nees	Leaves	Methanol	845 mg/kg	CCl_4	SGOT, SGPT, and ALP	[83]
Asteraceae	*Wedelia chinensis* L.	Leaves	Ethanol	200 mg/kg	CCl_4	AST, ALT, ALP, protein, and bilirubin	[84]
Fabaceae	*Cassia fistula*	Seeds	Methanol	200 and 400 mg/kg	PCM	SGOT, SGPT, ALP, and bilirubin	[85]

Contd...

Table 2: Contd...

Family	Name of the plant	Plant parts used	Extract used	Oral dose (mg/kg)	Hepatotoxicity inducing agents	Biochemical and histopathological parameter studied	Reference
Fabaceae	*Bauhinia racemosa* Lam.	Bark	Methanol	NA	CCl_4 and PCM	SGPT, SGOT, SOD, GSH, and TBARS	[86]
Fabaceae	*Bauhinia variegata* L.	Stem bark	Methanol	100 and 200 mg/kg	CCl_4	AST, ALT, ALP, and GGT	[87]
Scrophulariaceae	*Scrophularia hypericifolia*	Aerial parts	Ethanol	250 and 500 mg/kg	PCM	ALT, GGT, AST, and ALP	[88]
Phyllanthaceae	*Phyllanthus urinaria*	Whole plant	Methanol	200 mg/kg	Acetaminophen	Cytochrome P450 CYP2E1 protein	[89]
Phyllanthaceae	*Phyllanthus emblica*	Fruits	NA	100 mg/kg	CCl_4	GSH	[90]
Liliaceae	*Allium cepa*	Fresh bulbs	Aqueous	100, 300 and 600 mg/kg	Ethanol	ALT, ALP, AST, and TB	[91]
Moraceae	*Ficus carica*	Leaves, fruit, and roots	Petroleum ether extract, aqueous extract, and methanolic extract	NA	Rifampicin	NA	[92]
Rhamnaceae	*Ziziphus mucronata*	Leaves	Methanol	200 mg/kg	Dimethoate	SGOT, TBARS, SGPT, GSH, SOD, tocopherol, HDL, LDL, CHOL, TL, TGA	[93]
Lamiaceae	*Salvia miltiorrhiza*	Dried pulverized roots	Ethanol	50 mg/kg	CCl_4	Induce apoptosis of hepatic stellate cells (HSCs)	[94]
Malvaceae	*Hibiscus rosasinensis*	Flower	Aqueous	80, 160 and 240 mg/kg	Mixture of cholesterol and cholic acid with coconut oil	AST, ALT, ALP	[95]
Loranthaceae	*Dendrophthoe falcata*	Leaves	Aqueous and ethanol	100 mg/kg	CCl_4	AST, TP ALP, and ALT, TB	[15]
Asteraceae	*Bidens pilosa*	Dried aerial parts	Ethanol	15 mg/kg	CCl_4	AST, ALT, and LDH	[96]
Fomitopsis Deae	*Antrodia cinnamomea*	Fruiting bodies and mycelia	Aqueous extract and ethanol	1250 mg/kg	CCl_4	induced elevation of expression of hepatic mRNAs, i.e., MMP-9, TNF-α, KLF-6, and TGF-β1 levels	[97]
Cyperaceae	*Cyperus rotundus*	Leaves	Methanol	200 mg/kg	CCl_4	SGOT, SGPT, ALP	[98]
Malvaceae	*Hibiscus sabdariffa*	Aqueous extract	Aqueous	NA	CCl_4	ALT, AST, and ALP	[99]
Polygonaceae	*Rheum palmatum*	Dried root	Ethanol	400 mg/kg	CCl_4	ALT, AST, HA, and laminin (LN)	[100]
Araceae	*Amorphophallus paeoniifolius*	Tubers	Aqueous	300 mg/kg	PCM	sGPT, serum glutamic	[101]
Apiaceae	*Petroselinum crispum*	Leaves	Aqueous and methanol	200 mg/kg	STZ	ALP, TBARS, and GSH	[102]
Loranthaceae	*Loranthus parasiticus*	Leaves	Ethanol	100 mg/kg	D-galactosamine and CCl_4	SGPT	[103]
Fabaceae	*Trigonella foenum-graecum*	Dried seeds	Ethanol	20-100 mg/kg	TAA	ALP and GGT	[104]
Fabaceae	*Tephrosia purpurea*	Root	Ethanol	50-200 mg/kg	CCl_4	Induce apoptosis of hepatic stellate cells (HSCs)	[94]
Oxalidaceae	Oxalis corniculata	Whole plants	Ethanol	100 mg/kg	PCM	SGOT, SGPT, and ALP	[105]
Fabaceae	*Indigofera tinctoria*	Leaves	Methanol	75, 150, 300 mg/kg	PCM	TBARS, SOD, CAT, and GSH	[106]
Malvaceae	*Alcea rosea*	Aerial parts	Aqueous methanol	200 mg/kg	PCM	TB, DB, ALP, and AST	[107]

Contd...

Table 2: Contd...

Family	Name of the plant	Plant parts used	Extract used	Oral dose (mg/kg)	Hepatotoxicity inducing agents	Biochemical and histopathological parameter studied	Reference
Fabaceae	*Cajanus cajan*	Whole plant	Methanol	NA	CCl_4	SGOT, CHL, and SGPT	[108]
Solanaceae	*Cestrum nocturnum*	Leaves	Aqueous ethanol	250 and 500 mg/kg	PCM	SGOT, SGPT, ALP, AST, ALT, and LDH	[109]
Convolvulaceae	*Convolvulus arvensis*	Whole plant	Ethanol	200 and 500 mg/kg	PCM	ALP, ALP, AST, and TB	[110]
Fabaceae	*Glycyrrhiza glabra*	Roots	Aqueous	2 mg/kg	CCl_4	SOD, GST, CAT, GSH, and GSH-Px	[111]
Convolvulaceae	*Ipomoea staphylina*	Leaves	Hydroalcohol	200 mg/kg	CCl_4	ALP, SGOT, AST, CHL, ALT, SGPT	[28]
Malvaceae	*Malva parviflora*	Whole plant	Methanol	250 and 500 mg/kg	PCM	ALT, TP, AST, and ALP	[112]
Ranunculaceae	*Nigella sativa*	Seeds	Alcohol	NA	Galactosamine/ lipopolysaccharide	ALP, ALT, TB, AST, and TP	[113]
Oleaceae	*Fraxinus rhynchophylla*	Whole plant	Ethanol	100 and 500 mg/kg	CCl_4	GOT, GPT, CAT, SOD, and GPx	[114]
Polygonaceae	*Rumex dentatus*	Whole plant	Aqueous/ methanol	250 and 500 mg/kg	PCM	ALP, ALT, TB, and AST	[115]
Amaranthaceae	*Suaeda fruticosa*	Leaves	Aqueous/ methanol	500 and 750 mg/kg	PCM	SGPT, ALP, ALT, SGOT, AST, TP, and TB	[116]
Lamiaceae	*Thymus linearis*	Leaves	Aqueous/ether	250 and 500 mg/kg	PCM and CCl_4	SGOT, ALT, SGPT, TB, ALP, and AST	[117]
Boraginaceae	*Trichodesma sedgwickianum*	Leaves	Ethanol	400 mg/kg	CCl_4	GSH, ALP, SOD, AST, CAT, TB, ALT, and TP	[118]
Vitaceae	*Vitis vinifera*	Roots	Ethanol	200 mg/kg	CCl_4	SGPT, SGOT, ALP, and TB	[119]
Acanthaceae	*Hygrophila auriculata*	Roots	Aqueous	100 mg/kg	CCl_4	MDA, GSH, protein, bilirubin, SGOT, ALP, and SGPT	[120]
Lamiaceae	*Ocimum gratissimum*	Fresh leaves	Methanol	40 mg/kg	CCl_4	ALT, AST, and ALP	[121]
Fabaceae	*Bauhinia purpurea*	Leaves	Ethanol	50 and 250 mg/kg	PCM	ALT, ALP, and AST	[122]
Plumbaginaceae	*Plumbago zeylanica*	Aerial parts	Methanol	300 mg/kg	PCM	TB, SGPT, SGOT, and ALP	[123]
Salicaceae	*Salix caprea*	Flowers	Ethanol	150 mg/kg	CCl_4	ALT, AST, ALP, albumin, TB, TG, urea, creatinine, TB, TBARS, and GSH	[29]
Bignoniaceae	*Tecomella undulata*	Aerial parts	Aqueous/ ethanol	100 and 200 mg/kg	PCM	AST, GSH, SGOT, SOD, SPGT, CAT, GSH-Px, GST, ALP, and ALT,	[108]
Anacardiaceae	*Pistacia integerrima*	Bark	Ethyl acetate	NA	PCM	ALP, ALT, and AST	[124]
Scrophulariaceae	*Scoparia dulcis*	Leaves	Ethanol	500 and 1000 mg/kg	CCl_4	SGPT, TB, ALT, ALP, SGOT, and AST	[125]
Verbenaceae	*Stachytarpheta jamaicensis*	Whole plant	Ethanol	200 mg/kg	CCl_4	SGPT, TB, ALP, SGOT, AST, TP, CHL, and ALT	[126]
Lamiaceae	*Ocimum tenuiflorum*	Leaves	Alcohol	200 mg/kg	PCM	ALP, ALT, SGOT, AST, and SGPT	[127]
Mimosaceae	*Mimosa pudica*	Leaves	Methanol	200 mg/kg	CCl_4	AST, SGOT, ALT, SGPT, TP ALP, and TB	[128]
Rubiaceae	*Kohautia grandiflora*	Leaves	Aqueous	300 mg/kg	PCM	TP ALP, TB, ALT, and AST	[129]
Cupressaceae	*Juniperus communis*	Fruits	Ethanol	200 mg/kg	PCM and azithromycin	SGOT, TB, SGPT, and ALP	[130]
Oleaceae	*Fraxinus rhynchophylla*	Stem barks	Ethyl alcohol	400 mg/kg	CCl_4	ALT, AST, MDA, SOD, GSH, and GSH-Px	[13]

Contd...

Table 2: Contd...

Family	Name of the plant	Plant parts used	Extract used	Oral dose (mg/kg)	Hepatotoxicity inducing agents	Biochemical and histopathological parameter studied	Reference
Saururaceae	*Saururus chinensis*	Whole plant	Ethanol	70 mg/kg	CCl_4	AST, ALT, ALP, CHL, SOD, CAT, MDA, and GSH	[131]

SGOT=Serum glutamic oxaloacetic transaminase, SB=Serum bilirubin, SOD=Superoxide dismutase, GST=Glutathione S-transferase, ALP=Alkaline phosphatase, GPT=Glutamic pyruvic transaminase, ALT=Serum alanine aminotransferase, AST=Aspartate aminotransferase, SALP=Serum alkaline phosphatase, MDA=Malondialdehyde content, GSH=Glutathione, GSH-Px=Glutathione peroxidase, TG=Triglycerides, GPT=Glutamic pyruvic transaminase, TB=Total bilirubin, TBARS=Lipid peroxidation (thiobarbituric acid reactive substance), GSH=Reduced glutathione, ALB=Albumin, GR=Glutathione reductase, SALP=Serum alkaline phosphatase, GGT=Gamma glutamyl transferase, SALT=Serum aspartate amino transaminase, GPx=Glutathione peroxidase, GR=Glutathione reductase, CHL=Cholesterol, LDH=Lactate dehydrogenase, SGPT=Serum glutamate pyruvate transaminase, TP=Total protein, GOT=Glutamic oxaloacetic transaminase, CAT – catalase, TB=Total bilirubin, NA=Not applicable, CPF=Organophosphorous insecticide chlorpyrifos, TAA=Thioacetamide, d-GalN/LPS=d-galactosamine/lipopolysaccharide, INH=Isoniazid, RIF=Rifampicin, N/A=Not available

Salix caprea (*Salicaceae*)

Salix caprea belongs to the *Salicaceae* family.[29] It is usually refers to as goat willow or pussy willow or great sallow, which is a predominant species of willow in Europe and Western and Central Asia. Previous studies have shown that the plant has many biological prospects such as anti-inflammatory and anti-inflammatory as well as antioxidant activity.[47,139] *S. caprea* has been used by traditional healers for treating varieties of diseases in both human and animals, commonly used to relieve fever, headaches, stomachache, and constipation.[29] Qualitative analysis of the plant extract indicated the occurrence of bioactive ingredients such as phenolic and flavonoids as the predominant compounds. Flavonoids included quercetin, rutin, and luteolin-7-glucoside, while phenolic compounds identified included salignin and catechins.[140]

Wahid *et al*. assessed the hepatoprotective potential of ethanolic extract of *Salix subserrata* Willd flower in CCl_4-induced liver toxicity.[29] The ethanolic extract of this plant meaningfully decreased the levels of serum enzymes, indicating that the plant extract could actually restore the structural integrity of the plasma membrane or reverse hepatic tissue damage caused by CCl_4 toxicity. Antioxidant activity exhibited by this plant extract could be attributed to its hepatoprotective property, which scavenged the free radical metabolites of CCl_4 that consequently lead to lipid peroxidation and membrane destabilization and later cause liver cell damage.

Caesalpinia crista (*Fabaceae*)

Caesalpinia crista is a family of *Fabaceae*, genus of flowering plants in the legume family, typically recognized as Karanja in Hindi, a broad shrubby perennial climber distributed all over India in the plains on wasteland and coastal areas up to an altitude of 1000 m in the hills.[141] *C. crista* contains several bioactive compounds such as saponins, flavonoids, alkaloids, and glycosides. This plant has medicinal use such as anti-inflammatory, antimalarial, anti-jaundice, anthelmintic, antidiabetic, antiperiodic, and antipyretic.[61,142] In a research conducted by Mishra *et al.*, the hepatoprotective activity of ethanolic *C. crista* leaves extracts in PCM-induced hepatotoxicity in rats was investigated. The treatment of ethanolic extract (200 and 400 mg/kg) displayed substantial decrease in higher levels of TB and serum marker enzymes and TGA unlike the positive control group. Based on these findings, it was established that the ethanolic *C. crista* leaves extracts demonstrated favorable hepatoprotective properties against PCM-induced liver toxicity in rats.[61]

Alocasia indica (*Araceae*)

Alocasia indica is commonly cultivated in the tropical and subtropical regions, especially in West Bengal, Assam, Maharashtra, and Southern India. The plant is a perennial herb with an altitude of about 5 m.[17] The tuber part of the *A. indica* plant is edible which is often consumed as a common vegetable because it is cheap and easily available among the general population. *A. indica* is conventionally used in the treatment of spleen and abdomen-related ailments. The edible tuber part of the plant is commonly utilized as vegetable among Indian people although their research focus is on the nonedible leaf part of the plant. Recently, Pal *et al.*[14] assessed the hepatoprotective activity of ethanolic and aqueous extract of *A. indica* tuber against CCl_4-induced hepatic injuries in male Albino Wistar rats. From their findings, biochemical analysis revealed the different pharmacological ingredients such as saponins, alkaloids, glycosides, tannins, and flavonoids as well as SOD and CAT enzyme activities in both ethanolic and aqueous extracts. Ethanolic extract revealed higher flavonoid and phenolic contents as well as greater antioxidant property than the aqueous extract. Both the aqueous and ethanolic extracts exhibited potent hepatoprotective activities in *in vivo* study. Findings from this study indicated the antioxidant prospect of this plant extract for pharmaceutical consideration in designing liver diseases' drugs.

Opuntia ficus-indica (*Cactaceae*)

Opuntia ficus-indica (*Cactaceae*) is a species of cactus commonly used for fruit production that has long been a house-trained crop plant essential in agricultural economies distributed in the arid and semiarid parts of the world. It is probably believed to have originated from Mexico. It is often used livestock feed as a vegetable forage resource during water shortage and shortage of herbaceous plants.[143] Most scientific medicinal research studies involve the leaves (cladodes) rather than the fruit. The hepatoprotective potential of aqueous extract (2 mL/kg) from cactus cladodes in CCl_4-induced toxicity in Wistar male rats was examined.[54] The findings from this study displayed a noteworthy decrease in AST and ALT levels in the group treated with aqueous extract of *O. ficus-indica* contrary to the group where hepatotoxicity was induced treated with CCl_4.

Cyathea gigantea (*Cyatheaceae*)

Cyathea gigantea (Wall. ex. Hook.) is a tree fern which is usually distributed in the moist open areas of Thailand, Sri Lanka, Northeastern to Southern India, Western Java, and Nepal. This plant has the capacity to grow up to 20 m[49,144] Kiran *et al.*[49] have reported on the hepatoprotective effect of methanolic of *C. gigantean* leaf extract in PCM-induced toxicity in Wistar Albino rats. It was noted that the PCM intoxication led to histological and biochemical hepatic damage in the experimental rats. On the other hand, the treatment with methanolic *C. gigantean* leaf extract decreased the elevated levels of ALP, serum glutamic oxaloacetic transaminase, TB, and serum glutamate-pyruvate transaminase; in addition, it also reversed the hepatic damage by restoring the structural

integrity of the plasma membrane. The phytochemical screening showed that the leaf extract of *C. gigantean* comprises flavonoids, triterpenes, phenols, sterols, and saponins. These bioactive compounds might be responsible to its hepatoprotective potential. The findings from this study revealed the hepatoprotective potential of *C. gigantean* in PCM induced-hepatotoxicity model in rats.

Phoenix dactylifera (*Arecaceae*)

Phoenix dactylifera which is commonly referred to as date palm is regularly used in the northern parts of Nigeria, Middle-Eastern countries, and Arabian for liver ailment-related treatment with clinical symptoms such as jaundice.[52] Previous studies have shown that the fruits extract protects the liver from toxins and alcohol damage.[145] Okwuosa *et al*.[52] assessed the hepatoprotective potential of methanolic *P. dactylifera* fruit extracts (date palm) in TAA-induced toxicity in male rats. From their results, it was found that the methanolic fruits extract of the plant displayed substantial hepatoprotective capability because of the reduction in the hepatocellular enzymes levels of the test groups as compared to the TAA-induced group. The potential of the extract to upset the rise in serum bilirubin and ALP induced by TAA suggests it prospect in reversing the plasma membrane damage.[52] Qualitative screening of the plant extract showed the presence of tannins, flavonoids, saponins, terpenoids, carbohydrates, steroids, proteins, and glycosides. Flavonoids have been reported to have membrane-stabilizing capability.[146] Therefore, it is wise to conclude that the membrane stabilizing effect of *P. dactylifera* extract could be due to the presence of flavonoid in it. However, the biochemical mechanism of the hepatoprotective effect of the *P. dactylifera* was not investigated in this study. The bioactive compound in fruit extract β-sitosterol was assumed to be responsible for it action.[147] In addition, flavonoid was proposed to be responsible for the hepatoprotective role via cytochrome P450 aromatase inhibition.[148] Similarly, Al-Qarawi *et al*.[149] documented the hepatoprotective property of aqueous of flesh and pits of dates extracts (*P. dactylifera* L.) against CCl_4-induced toxicity in rats.

Convolvulus arvensis (*Convolvulaceae*)

Convolvulus arvensis is a creeping weed that is widely spread in Asia.[150] This plant species belongs to *Convolvulaceae* family. The plant can form 5 cm thick carpets-off the ground when not climbing and this plant is commonly used as laxative. The plant extract is used in skin diseases, cough, jaundice, and flu. In addition, it could also be used for treating painful joints, swelling, and inflammation. Recently, Ali *et al*.[110] documented the hepatoprotective potential of ethanolic extract of *C. arvensis* (200 and 500 mg/kg) in PCM-induced toxicity in rats. There was a substantial decrease ($P < 0.05$) in the increased levels of TB and hepatic enzymes observed when ethanolic extract of *C. arvensis* was treated with PCM-induced rats. The main phytochemical components of the *C. arvensis* were quercetin and kaempferol. Quercetin is a flavonoid that has been established to be a hepatoprotective agent.[151]

BIOACTIVE MOLECULES WITH HEPATOPROTECTIVE POTENTIALS

From previous studies, several biomolecules have been isolated from plants with promising hepatoprotective potential. However, clinical trials of these pure compounds have not been thoroughly carried out on humans. Some of the bioactive compounds have several biological properties such as antiviral, antioxidant, anticancer, antiaging, antifibrotic, antidiabetic, and anti-inflammatory potentials, due to biomolecules including resveratrol, curcumin, silymarin, glycyrrhizin, and quercetin that they possess [Table 3].[108,152-161]

Table 3: Examples of reported phytochemical compounds with hepatoprotective potential

Phytochemical compounds	Plants
Glycyrrhizin	*Glycyrrhiza glabra*
Resveratrol	*Hygrophila auriculata*
Curcumin	*Curcuma spp.*
Colchicine	*Colchicum autumnale*
Silymarin (silybin)	*Silybum marianum*
Quercetin	*Hibiscus vitifolius*
Fumaric acid	*Sida cordifolia*
Coumarins	*Artemisia abrotanum*
Schizantherin A	*Schisandra chinensis*
Kutkoside	*Picrorhiza kurroa*
Catechin	*Anacardium occidentalis*
Papyriogenin	*Tetrapanax papyrifer*
Cronin	*Gardenia jasminoides*
Syringopicroside	*Syringa oblata*
Piceid	*Polygonum cuspidatum*
Gomishins	*Schisandra chinensis*
Saikosaponin	*Bupleurum falcatum*
Cosmosiin	*Cupressus sempervirens L.*
Patuletin	*Ficus ingens*

CONCLUSIONS AND FUTURE PROSPECTS

Health issues have become a societal problem although we all pay much attention to our health. The liver performs a critical function in the body, and liver injuries or diseases have become one of the most common health issues globally. Excessive alcohol consumption and poor eating habits, the use of herbal supplements, as well as microbial infections, autoimmune diseases, cancers, metabolic diseases, and the abuse of certain drugs are the major causative agents of liver damage. Hence, protection of the liver against the above-mentioned factors is imperative.

Meanwhile, discovering novel drugs effective for liver damage has become imperative especially in view of the fact that the available modern medicine used for treating the different kinds of liver diseases is either inadequate or associated with kidney function side effects Thus, it is necessary to produce new alternative plant-based hepatoprotective drugs. Most of the plant-based medicines used for treating liver diseases are designed based on their antioxidant-related properties and hepatoprotective activities. These are the main scientific mechanisms that the novel drugs used to treat liver diseases are based upon with the least side effects on the kidney. Therefore, more investigations are needed to evaluate the potentials of new candidate phytochemicals for the production of more effective hepatoprotective drugs.

Herbal remedies have gained global attention because 50% of people in developing countries, who suffer from one liver disease or the other, rely on them for treatment. Most of the available herbal extracts on the market have shown significant promise in relieving the symptoms of liver injury or disease. Nevertheless, the scientific validation of the herbal extracts has not been established; hence, it will be necessary to conduct additional research, especially in this area, to standardize the preparation and administration of the herbal extracts for efficacy and safety. In the same vein, it will be essential to subject such herbal products to preclinical studies and subsequently to clinical trials. This will ascertain the actual healing value of these natural herbal products, and the standard dosage regimen determined based on clinical trials will also be helpful in drug designing and administration. Furthermore, the traditional medicine approach toward drug discovery and design can make available several vital drugs for treating diverse kinds of diseases.

Isolating active principles and their use as drugs is expensive and time-consuming. However, plant-based drugs (individual or combination

plant extracts) should be made available for treating liver diseases with the emphasis on restoring the structural integrity of the hepatic cell membrane. A single plant extract is not usually effective in the treatment of all different kinds of liver disease. Hence, it could be necessary to formulate an herbal mixture from two or more plant extracts to improve the efficacy of the treatment. It would also be important to carry out further research especially toxicity assays with the intention of ensuring the safety of the plant mixture because it is very possible that one of the plant extracts could be toxic and consequently antagonize the efficacy of the others in the extract mixture. In addition, since most plant extracts are used in developing countries by poor people in the rural areas, it will be necessary to enlighten traditional healers about good hygiene in plant preparation and ensure prevention and/or elimination of contamination in the preparation of the herbal extracts.

Finally, to produce more effective plant-based hepatoprotective drugs, it will be necessary to carry out further studies on the structural modifications of the active principles derived from herbal extracts using computational chemistry techniques.

Financial support and sponsorship

We are grateful to the South Africa Medical Research Council (SAMRC) and University of Fort Hare for their financial supports.

Conflicts of interest

There are no conflicts of interest.

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