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Recent Insights into Some Emerging Natural Resources with Remarkable Hepatoprotective Potentials

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Abstract

Liver an accessory digestive organ present in vertebrates results in detoxification of the metabolites, synthesis of protein, generation of necessary biochemicals such as bile, as well an energy reservoir in form of glycogen. Liver disease also named as hepatic disease creates a toll in the hepatic management causing an effect on overall functions of Liver. The motto of our present study is based on the hepatotoxicity management of liver based on traditional herbal medicine. Liver diseases has hundreds of symptoms among which we addressed specifically oxidative stress, anomaly in protein distribution, fat related peripheral catabolism, concurrent viral hepatitis, increased redox ratio, retention of liver cell water and viral proteins, effected cell mediated immunity, fibrogenesis, and inflammation. This review article describes the various natural resources (plant extracts) of diverse families having hepatoprotective effects and the active constituents responsible for it.

Keywords: Liver, Natural, Plants, Extracts, Hepatotoxicity, Hepatoprotective

1. Introduction

Liver has three well-known properties to get involve in metabolism, have a high potential of regeneration and recovery from injury. The acute and severe cases of liver injury lead to life-threatening clinical syndromes including jaundice, severe coagulopathy, and increased rates of mortality. Still developing, medical tasks for elucidating the pathophysiological mechanisms and development of efficient therapy are going under consideration especially for severe hepatic injury [1]. Traditionally, various herbal medicine is studied to maintain the health, to prevent the disease condition and also proven for the cure of diseases. As the hepatotoxicity is very common in case of liver and can occur due to different causes which are studied before the management. Liver function tests should be performed for the proper diagnosis. In clinical practice, to recognize the hepatotoxicity, and for the preventive measures, steps are taken [2].

2. Monitoring of the symptoms

Symptoms like nausea, anorexia, malaise, fatigue, and right upper abdominal discomfort. Specific symptoms such as itching or jaundice should prompt consideration of hepatotoxicity while using the drug [3].

3. Considering a careful history

Clinical history of the patients should be checked along with the drugs being used, and a detailed history for the use of prescribed and non-prescribed over-the-counter herbal and other medications or remedies, with dates and amounts [4].

4. Drug-induced hepatic injury

If a drug gives allergic reaction during the therapy, it needs immediate withdrawal of suspected drugs. If in the use of allergy corticosteroids, which are not under controlled trial for efficacy, hence with that urodiol is given frequently for the cholestatic liver injury. But only N-acetyl cysteine is used for the acetaminophen poisoning. Liver transplanting was the final solution if coagulopathy or encephalopathy of liver is present [5].

5. Mechanisms of Liver damage

5.1) Increasing oxidative stress

Oxygen metabolism is the basic process for the liver functions and its mechanism. Alcohol toxicity may be associated with increased oxidative stress and free radical associated injury. Generation of oxygen metabolites such as superoxide (O_2^-) hydrogen peroxide (H_2O_2) and hydroxyl radicals (OH^-) are believed to be important in the pathogenesis of alcoholic liver injury [6].

5. 2 Disturbing protein metabolism

The protein synthesis takes places in the liver and indirect disturbance in the mechanism cause one of the major disturbances in liver functioning. Acetaldehyde (the major intermediate metabolite of alcohol protein route to acetate production) induces lipid peroxidation and also acetaldehyde causes protein adducts formation, further disrupting cytoskeletal and membrane function [7]. Alcohol induces an immunologic attack on hepatocytes that are antigenically altered by alcohol or by acetaldehyde responsible for alteration in hepatic proteins. Hepatocellular steatosis arises as a result of the following facts A) Shunting of normal substrates away from catabolism toward lipid biosynthesis, owing to generate excess reduced nicotinamide and adenine dinucleotide by two major enzyme of alcohol metabolism, that is alcohol dehydrogenase and acetaldehyde dehydrogenase (generating acetate). B) Impaired assembly and secretion of lipoprotein [8].

5.3 Peripheral catabolism of the fat increased

Increasing the level of interleukin 8 and chemo-attractants of neutrophils by infiltration of the liver is quite common in alcoholic hepatitis and it is assumed that the activated neutrophils release toxic oxygen metabolites. Alcohol is also responsible for the increase in liver fat [9].

5. 4 Concurrent viral hepatitis

Particularly hepatitis-C, is a major factor that accelerates liver disease in alcoholics. The prevalence of hepatitis-C in patients with alcoholic disease is about 30% [10].

5.5 Increased redox ratio

NAD redox ratio in hepatocytes results in increased redox ratio of lactate pyruvate causing lactic acidosis with a number of metabolic consequences such as fatty liver, collagen formation, occurrence of gout, impaired gluconeogenesis and altered steroid metabolism [11].

5.6 Retention of liver cell water and proteins

Hepatomegaly and hepatocyte are caused by alcohol and are responsible for water retention [12].

5.7 Hypoxia

Hepatocellular necrosis leads to hypoxia due to chronic ingestion of alcohol causing hepatocellular necrosis in centrilobular zone [13].

5.8 Immunological mechanism

Cell mediated immunity is impaired in alcoholic liver disease. Ethanol causes direct immunologic attack on hepatocytes. Immunological mechanism may also explain genesis of Mallory's alcoholic hyaline though more favored hypothesis for its origin is aggregation of intermediate filaments of prekeratin due to alcohol induced disorganization of cytoskeleton [14].

5.9 Fibrogenesis and inflammation

The mechanism of fibrosis and inflammatory response in alcoholic liver disease are uncertain. The possible mediators are lymphokines and monokines. The major stimulant for fibrogenesis is cell necrosis. All forms of collagen are increased and therefore show increased transformation of fat storing cells into myofibroblasts and fibrocytes. Leukotrienes which are important mediators of inflammation are produced by alcohol-damaged hepatocytes resulting in inflammatory reaction at the affected areas [15].

Since, many toxic chemicals induce liver damage by lipid peroxidation or oxidative damage to DNA and reduction in the levels of glutathione, assessment of anti-oxidant property is useful. Anti-oxidant property of plant drugs is studied using liver homogenates, isolated liver cell membranes and DNA in the process leading to cirrhosis, accumulation of connective tissue and parenchymal regeneration are the following competing events. Therefore, the search for agents to prevent liver cirrhosis is also focused on inhibition of excessive connective tissue formation in the liver. Fibro-suppressive effects on protein hydroxylation by inhibitors also can be screened [16].

6. Management of hepatotoxicity

Management is the main part for the hepatotoxicity as liver is the vital organ and has the capacity to regenerate and repair by using the natural herbal plants and even the diet can improve liver toxicity. The main aim of this review is to study different mechanism and effect on the hepatotoxicity [17]. **Table 1** describes the various plants of diverse families having hepatoprotective effects and the active constituents responsible for it.

Table 1: Hepatoprotective potentials of various plants and their active constituents.

S. No.	Plant	Family	Active constituents	Parts used
1.	*Andrographis paniculata*	Acanthaceae	Andrographolide, Kalmeghin, Flavanoids, Diterpenoids, Polyphenols	Leaves, Aerial part
2.	*Adhatoda vasica*	Acanthaceae	Glycosides, Flavonoids, Benzonoids, Phenolic compounds, Naphthoquinone, Triterpenoids.	Leaves
3.	*Boerrhavia diffusa*	Nyctaginaceae	Glycoside, Flavonoids, Sterols	Roots
4.	*Calotropis procera*	Asclepiadaceae	Procesterol, Cyclosadol	Flower
5.	*Curculigo orchioides*	Amaryllidaceae	Curculigenin, Curculigenin A	Rhizome
6.	*Fumaria indica*	Fumariaceae	Carbohydrate, Alkaloids, Steroids, Saponins	Whole plant
7.	*Garcinia cambogia*	Clusiaceae	Camboginol, Cambogin, Erythro-L-hydroxy Citric acid	Rind of fruit
8.	*Luffa acutangula*	Curcurbitaceae	Flavonoids, Phenolic, Glycosides, Carbohydrates, Saponins	Fruit
9.	*Mamordic subangulata*	Curcurbitaceae	Momordicine, Saponin, Carotene	Leaf
10.	*Naragamia alata*	Meliaceae	Alkaloid, Steroid, Saponin	Plant

11.	*Taraxacum officinale*	Asteraceae	Tannins, Saponins, Alkaloids, Phenolic compounds, Glycosides, Flavonoids	Plant
12.	*Baliospermum montanum,*	Euphorbiaceae	Axillarenic acid, 12-deoxy-5β-hydroxyphorbol-13-myristate, 13-palmitate, 12-deoxyphorbol13-palmitate, baliospermin, montanin	Root, Seeds, Leaves
13.	*Azardirchata indica*	Meliaceae	Glycoproteins, Triterpines, Limonoids, Flavonoids, Phenols, Tannins, Nimbins, Saponins, Catechins, Azadirachtin, Gallic acid	Plant
14.	*Allium sativaum*	Amaryllidaceae	Organosulfur compounds	Root
15.	*Silybum marianum*	Astaraceae	Silymarin, Lignans, Silybin, Silydiania, Silychristine	Seeds
16.	*Sida cordifolia*	Malvaceae	Fumaric acid, Organic compounds, Ephedrine, Pseudoephedrine	Roots, Leaves, Seeds, Whole plant
17.	*Schisiandra chinensis*	Simmondsiaceae	Wuweizisu, Lignans	Leaves
18.	*Pinus maritime*	Gymnospermeae	Glycoside, Pycnogenol	Fruits
19.	*Phyllanthus amarathus*	Phyllanthaceae	Polyphenols, Phyllanthin	Fruits, Whole plant
20.	*Rubia cordifolia*	Rubiaceae	Glycoside, Rubiadin, Hydroxytranquinone	Roots
21.	*Gincago biloba*	Ginkgoaceae	Polyphenols	Seeds
22.	*Gossypium herbaceum*	Malvaceae	Gossypol, Polyphenols	Roots
23.	*Camellia sinensis*	Theaceae	Polyphenols, Catechin	Leaves
24.	*Nigella sativa*	Ranunculaceae	Polyphenols, Thymoquinone	Seeds
25.	*Larrea tridentate*	Zygophyllaceae	Resins, Nordihydroguiarectic acid	Leaves
26.	*Buddleja officinalis*	Scorphulariaceae	Glycosides, Acetosides, Vitamin P	Flower, Buds
27.	*Ocimum basilium*	Lamiaceae	Phenolic acids, Rosmarinic acid	Flower, Seeds Leaves, Whole plant
28.	*Peumus boldus*	Monimiaceae	Alkaloids, Boldine	Leaves
29.	*Mangifera indica*	Anacardiaceae	Triterpene, Luoeol	Whole part
30.	*Hibiscus sabdariffa L.*	Malvaceae	Polyphenols, Protocatechuic acid, Vitamin C	Leaves, Fleshy red calyx
31.	*Magnolia officinalis*	Magnoliaceae	Polyphenols, Magnolol	Bark, Flower, Buds
32.	*Gardenia jasminoides*	Rubiaceae	Iridoid glycoside, Geniposide	Fruits
33.	*Eglets viscose Less.*		Flavonoid, Ternatin	Leaves
34.	*Corydalis saxicola*	Papaveraceae	Alkaloid, Dehydrocavidine	Aerial parts
35.	*Cistus laurifolis L.*	cistaceae	Flavoniods, Ternatin	Leaves
36.	*Eupatorium triplinerve*	Asteraceae	Thymohydroquinondiethyl ether	Leaves
37.	*Trigonella foenum*	Lamiaceae	Vitamin A, Vitamin C, Tocopherol, Total phenol, Lycopene, Carotenoid, Flavonoids	Leaves
38.	*Picrrorhiza kurroa*	Scrophulariaceae	Kurkin, Picroside, Vanilic acid, *D*-mannitol, Rosin, Apocynin	Roots, Whole plant
39.	*Tephrosia purpurea*	Papilionaceae	Alkaloids, Glycosides, Tannins, Phenolics, Triterpenoids	Whole plant
40.	*Sisbenia grandiflora*	Fabaceae	Vitamin C, Lenolic acid, Aspartic acid	Leaves
41.	*Termalia chebula*	Combretaceae	Chebulic acid, Gallic acid, Punicalagin, Geraniin, Phyllanemblinin E, Chebulagic acid, Chebulinic acid	Fruits
42.	*Moringa oleifera*	Moringaceae	Vitamin C, Calcium, Minerals	Leaves, Fruits, Seeds
43.	*Achillea millefolium*	Asteraceae	Isovaleric acid, Salicylic acid, Asparagines, Sterols, Flavonoids	Flower, Stem, Aerial part
44.	*Capparis spinosa*	Capparaceae	Alkaloids, Glycosides, Tannins, Phenolics, Triterpenoids, Flavanoids, Minerals, Saponins	Roots
45.	*Cassia occidentalis*	Solanaceae	Alkaloids, Glycosides, Tannins, Phenolics, Crysophenols, Emodin derivatives, Flavanoids, Occidentalins A and B	Roots, Leaves, Seeds
46.	*Cichorium intybus*	Asteraceae	Alpha–amyrin, Taraxerone, Baurenyacetate, Beta-sitosterol, Lactones, Vitamins, Minerals, Fats	Leaves, Roots
47.	*Solanum nigrum*	Solanaceae	Gentisic acid, Luteolin, Kaempferol, *m*-coumaric acid, Glycosides, Glycoproteins, Polysaccharides	Fruits, Whole plant
48.	*Tamarix gallica*	Tamaricaceae	Tamarixin, Tamarixetin, Tropin, 4-methylcoumarin, 3,3’di-o-methylellagic acid, Quecerol, Tamarixellagic acid	Leaves, Flowers
49.	*Terminalia arjuna*	Combretaceae	Tannis, Phytosterols, Magnesium, Saponins, Flavanoids, Zinc, Arjunone, Luteolin, Gallic acid, Ellagic acid, Argugenin, Calcium, Copper	Stem, Bark

50.	*Asteracantha longifolia*	Acanthceae	Lupol, Stigmasterol, Butelin, Fatty acids, Alkaloids	Whole plant, Roots, Seeds
51.	*Trachyspermum ammi*	Apiaceae	Thymol, *p*-cymim, Gamma-terpinene, Beta-pinene, Alpha-terpine	Leaves, Seeds, Fruits
52.	*Apium graveolens*	Apiaceae	Caffeic acid, Chlorogenic acid, Apiin, Apigenin, Rutaretin, Ocimene, Bergapten, Isopimpinellin, Alkaloids, Steroids	Seeds, Roots
53.	*Berberis lyceum*	Berveridaceae	Alkaloids, Cardioactive glycosides, Saponins, Tannins, Anthocyanins, Vitamins, Phytic acid, Minerals	Roots
54.	*Phyllanthus niruri*	Euphorbiaceae	Gallic acid, Phyllanthin, Ellagic acid	Whole plant
55.	*Cichorium intybus*	Asteraceae	Inulin, Sesquiterpene Lactones, Vitamins, Minerals,Fat, Mannitol, Latex	Whole plant
56.	*Cyperus rotundus*	Cyperaceae	Cyperene, Humulen, Beta-selinen, Zierone, Campholein aldehyde	Rhizomes
57.	*Eclipta alba*	Asteraceae	Hentricontanol, Heptacosanol, Protocatechuic acid, 4-Hydroxy-benzoic acid, Verazine, Ecliptalbine	Whole plant
58.	*Ipomoea turpethum*	Convulvulaceae	Resins, Saponins, Flavanoids, Steroids, Triterpenes, Etulinic acid, Betulin acid, Sitosterol, Glucose, Rhamnose	Aerial part
59.	*Oldenlandia corymbosa*	Rubiaceae	Geniposide, 6-alpha-hydroxygeniposide, Scandoside methyl ester, Asperuloside, Asperulosidic acid	Whole plant
60.	*Plumbago zeylanica*	Plumbaginaceae	Plubagin, Isoshinolone, Plumbagic acid, Trans-cinnamic acid, Vanillic acid, Indole-3-carboxaldehyde	Roots
61.	*Hygrophila spinosa*	Acanthaceae	Phytosterols, Fatty acids, Minerals, Polyphenols, Enzymes, Terpenoids, Flavanoids, Glycosides	Aerial part, Whole plant
62.	*Tephrosia purpurea*	Leguminaceae	Triterpenoids, Rotenoids, Sterols, Essential oils, Fixed oils, Flavonoids	Seeds, Roots, Bark, Whole plant

The herbal drugs or polyherbal combinations are the traditional approach towards the treatment of liver disfunction caused by viral hepatitis, alcohol, toxic drugs and plant toxins. The Silymarin that is extracted from *Silybum marianum*, andrographolide extracted from the *Andrographis paniculata*, curcumin extracted from the *Curcuma longa*, picroside and kutkoside taken from the *Picrorrhiza kurroa*, phyllanthin and hypophyllanthin taken from *Phyllanthus niruri*, glycyrrhizin extracted from *Glycyrrhiza glabra* are the traditional sources used in the treatment of liver diseases and represent the phytochemical constituents that have been studied for their chemical and biological profile and clinical efficacy [18]. These show hepatoprotection due to anti-oxidant effect. In case of the free radical scavenger studies, the extracts reduced the free radical oxygen in serum and liver due to the anti-oxidant properties which is justified by the increased serum concentration of glutathione and reduced lipid peroxidase in the liver [19].

Vitamins are required by the human body and considered as vital nutrients needed in specific amounts. They cannot be synthesized in a sufficient amount by the human body; so, they must be obtained from the diet. Thirteen different types of vitamins are known that are classified by their biological and chemical activity. Each one of them has a specific role in our body. Folic acid has a vital role in cell growth and development through many reactions and processes that occur in the body, *e.g.* histidine cycle, serine and glycine cycle, methionine cycle, thymidylate cycle, and purine cycle [20]. When the body becomes deficient in folic acid, all cycles that are mentioned above will become ineffective and lead to many problems, in addition to other problems such as megaloblastic anemia, cancer, and neural tube defects. Vitamin B_{12} has a vital role in cell growth and development through many reactions and processes that occur in the body. When the level becomes elevated or lower than the normal, the whole process will collapse because each process is linked to another. Deficiencies can be treated by increasing their consumption in diet or by supplement intake [21].

Silymarin is a plant-based formulation, a clinical drug with proven capacity shows effectiveness to guard liver from harmful hepatotoxins. Such pharmacological power was attributed to silymarin's inherent constituents with anti-oxidant, anti-inflammatory, and diuretic properties, as in other medicinal plants in nature [22]. Silymarin also has the capacity to show anti-lipid peroxidation and induced detoxification system, protector of cell against employed glutathione, reducer of leukotriene formation from unsaturated free acid, enhancer of protein synthesis, stabilizer of mast cells and regulator of immune functions. It inhibits cytoP_{450} detoxification system and prevents metabolism of toxic compound such as TAA [23].

7. Vitamin-C and Vitamin-E

Vitamin E acts by inhibiting lipo-peroxidative chain reactions needed for the lipid peroxidation. Vitamin-C and vitamin-E in combination gives the synergistic anti-oxidant action. The study results suggest that vitamin-C and vitamin-E affect liver regeneration by enhancing the functional role of hepatocytes. Lu reported a metabolomics analysis in POFS rats induced by PH. The citric acid cycle, branched-chain amino acids metabolism, fatty acid transport and metabolism, phospholipid metabolism, tryptophan metabolism, phenylalanine metabolism and purine metabolism became abnormal as metabolic pathways and potential biomarkers associated with POFS. Among these results, it is necessary to supplement the branched chain amino acids reduced by fatigue-induced glycogen depletion [24]. In this experiment, vitamin-C and vitamin-E were administered at doses of 250 mg/kg body weight per day dose can be maintained examining the residual liver functions. The capability of the liver is to fully regenerate after injury i.e. a remarkable phenomenon essential for the maintenance of its important functions in the control of metabolism and xenobiotic detoxification. The regeneration process is histologically well described, but the genes that orchestrate liver regeneration have been only partially characterized. The particular field of interest is cytokines and growth factors, responsible for controlling different phases of liver regeneration. Historically, their potential functions in this process were addressed by analyzing their expression in the regenerating liver of rodents. Functional studies has confirmed this predicted role by including neutralizing antibodies or siRNAs prior to liver injury or during liver regeneration and systemic delivery of recombinant growth factors. Use of mice that are genetically modified in liver regeneration studies has often shown unexpected functions of growth factors, including cytokines and their downstream signaling targets of liver regeneration. This review summarizes the results obtained by functional studies that have addressed the roles and mechanisms of action of growth factors and cytokines in liver regeneration after acute injury to this organ [25].

Oxidative stress has been a key causing factor of liver damage that is being induced by a variety of agents, and has shown a major contributing factor in almost all conditions compromising liver function, including ischemia-reperfusion injury (IRI), nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), liver fibrosis, liver cirrhosis, and hepatocellular carcinoma (HCC). In liver higher concentration of melatonin (N-acetyl-5-methoxytryptamine) accumulates, and the sole organ metabolizing circulating melatonin. Melatonin is one of the best anti-oxidants that protect liver, and its metabolites also have anti-oxidative function [26]. Through the radical scavenging ability and indirect stimulation of anti-oxidant enzymes melatonin exerts its antioxidative function directly. Various factors, including dosage, route, time and duration of administration, the type of oxidative-induced agent and species aging the anti-oxidative response from melatonin in liver. This indoleamine is also an effective and promising anti-oxidative choice for targeting liver IRI, NAFLD, NASH, fibrosis, cirrhosis, and HCC [27].

From *Bacopa monnieri* Linn. (Schrophulariaceae) the aerial parts; *i.e.* the EBM along with its ethanol extract was investigated for an in-site over *in-vivo* and *in-vitro* properties such as anti-oxidant and hepatoprotective effects. Preparations of EBM along with estimation of total phenolics were carried out. *In vitro* models allowed the study for anti-oxidant activity of EBM. Estimation of total phenolics was 47.7g of pyrocatechol equivalent per mg of extract. Extract shows reducing power based on concentration dependency. The following chemical reuptakes; *i.e.* anti-oxidant activity, nitric oxide scavenging activity and superoxide radical scavenging activity were also concentration dependent key-factors along with an IC_{50} value being 238.22 g/mL, 29.17 g/mL, and 22.92 g/mL, respectively. The activities found were comparable with the reference drugs. Now the animals (Wistar albino rats) were administered dose of paracetamol (500 mg/kg, p.o., once in a day for 7 days). EBM of 300 mg/kg/day and silymarin at dosage uptake of 25 mg/kg/day, the combination was administered to the rats treated with paracetamol for seven days [28]. Now the measurement of the effects due to EBM and silymarin on serum transaminases (SGOT, SGPT), alkaline phosphatase (ALP), bilirubin (Direct and Total), cholesterol (HDL and Total), and total protein were checked in the hepatotoxic rats. After that the lipid peroxidation (LPO), glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) were extracted to estimate their effects. EBM and silymarin shows ($p<0.05$) hepatoprotective effect by decreasing the action of serum enzymes, bilirubin, total cholesterol, *in-vivo* lipid peroxidation, responsible ($p < 0.05$) for providing a hike in the levels of GSH, CAT, SOD, and HDL cholesterol. EBM provides anti-oxidant effects on $FeCl_2$-ascorbate-induced lipid peroxidation in the paracetamol induced rat liver homogenate. The following results, suggests that EBM has the potential as protecting agent of the liver cells from paracetamol-induced liver damage, because of its anti-oxidative effect on hepatocytes, allowing elimination of deleterious effects due to toxic metabolites by paracetamol [29].

It appears that vitamins C and E administration promotes liver regeneration. Vitamin E has a suppressive effect on the increase in lipid peroxidation by inhibiting lipo-per-oxidative chain reactions. Recent studies have demonstrated that vitamins C and E have a marked synergistic anti-oxidant action. Similar results were observed in this study. In this experiment, vitamin C and vitamin E were administered at doses of 250 mg/kg body weight per day. It is possible that the action of these vitamins is dose-dependent. Based on our findings, it is likely that administration of vitamins C and E markedly promotes liver regeneration and reduces parenchymal hepatocyte damage after PH and continuous alcohol administration. Additional studies are required, such as assessing the effects of oral administration of vitamins C and E, as well as the amount of alcohol administered. We also need to examine the residual liver function of the rat over a longer period of time. Based on the ratio of liver mass relative to body weight, a possible influence of vitamins C and E on the promotion of liver regeneration cannot be excluded. Functional role of hepatocytes from our results suggest that vitamins C and E affect liver regeneration by enhancing the functional role of hepatocytes [30]. Lu reported a metabolomics analysis in POFS rats induced by PH. The citric acid cycle, branched-chain amino acids metabolism, fatty acid transport and metabolism, phospholipid metabolism, tryptophan metabolism, phenylalanine metabolism and purine metabolism became abnormal as metabolic pathways and potential biomarkers associated with POFS. Among these results, it is necessary to supplement the branched chain amino acids reduced by fatigue-induced glycogen depletion. This supplementation is useful for relieving fatigue and promoting recovery after surgery. Whether this also contributes to the protection of residual liver function should be studied. There is a need to clarify basic information on the role of oxidative stress in the onset of disease and ROS-related cytotoxicity and to continue to consider reasonable anti-oxidant therapies in the future effects of drugs during therapy consists of the immediate withdrawal of any and all suspected drugs. If a severe allergic reaction is observed, corticosteroids may be used, but no controlled trials have been performed to ascertain their efficacy. Similarly, ursodiol is frequently given for cholestatic liver injury, but it has not been subjected to careful study in this setting. Except for N–acetylcysteine for acetaminophen poisoning, there are no specific antidotes. The patient should be transferred to a liver-transplantation center if coagulopathy (as measured by an international normalized ratio of 1.5 or greater) or encephalopathy is present [31].

The study has concerned the hepatoprotective activity of aqueous extract of *Camellia sinensis* leaves and deducing its possible mechanism of action. Intraperitoneal administration of carbon tetrachloride/olive oil (50 % v/v, 0.5 ml/kg) in male Wistar rats (150-220 g) once daily for 7 days has induced

Liver damage by the extent of damage that was studied by assessing biochemical parameters such as alanine amino transferase (ALT), aspartate amino transferase (AST), alkaline phosphatase (ALP), total protein, and albumin in serum and concentrations of lipid peroxides (LPO), glutathione (GSH), catalase (CAT), and superoxide dismutase (SOD) in liver. Aqueous extract of the plant (100 mg/Kg and 200 mg/Kg) was administered orally to the animals that are showing hepatotoxicity, were induced by carbon tetrachloride and its effects on biochemical parameters were compared with animals administered with vitamin E (100 mg/Kg). Histopathological studies were also done [32]. The following doses of *Camellia sinensis* 100 mg/kg and 200 mg/kg results in significant reduction of serum hepatic enzymes and liver lipid peroxide that was been increased by carbon tetrachloride. The significant rise in serum total protein, albumin and liver GSH, SOD, and CAT was then with contrast to those in rats treated by carbon tetrachloride**.** Now the comparison of anti-oxidant activity of *Camellia sinensis* (100 mg/kg and 200 mg/Kg) with the effects of vitamin-E (100 mg/Kg) was checked. The inducing histopathological changes (congestion of central vein, centrilobular necrosis, and sinusoidal congestion) by carbon tetrachloride were reduced to a moderate extent in *Camellia-sinensis*-treated rats. Altogether, the effect from *Camellia sinensis* protects the liver from carbon-tetrachloride-induced damage. Probable mechanism of its action is its anti-oxidant property [33].

Preliminary evidences collected in this study by the observations made and measured shows the progression of the liver cirrhosis induced by TAA in rats can be intervened using the PN extract. This natural extract has shown potential to protect the liver by preventing actions of harmful events that are analogous with the TAA toxicity from occurrence. The effects are comparable to those of silymarin and the capability of the PN extract to preserve the liver's status quo of property, structure, and function against toxic exposure is encouraging and warrants further studies exploring the significance of its pharmacologic potential in treating the liver cirrhosis by mapping the molecular pathways of action [34].

8. Conclusion

In research a remarkable work has been done on the liver regeneration and its functioning. The herbal medicinal plants individually and in combination have also proved better result than the allopathic medicine. This review has explored the different parameters working on the liver regeneration. Numerous parameters are responsible for the regeneration of liver cell. Although a large number of herbal medicinal plants have been proven for regeneration of liver. In this review article studied 60 herbal medicinal plants which showed their effect in single and in combination also. The anti-oxidant property is mainly responsible which is shown by different flavonoids, alkaloids, glycosides, and other help in the regenerating liver. Ayurvedic preparations like liv52 and other already proven positive result in liver cirrhosis and other liver diseases. Different phytochemicals possess a wide range of activities, useful in protection against chronic diseases. For example, alkaloids protect against chronic diseases. Saponins protect against hypercholesterolemia and antibiotic properties. Steroids and triterpenoids show the analgesic properties. Vitamin E acts by inhibiting lipo-per-oxidative chain reactions needed for the lipid peroxidation. Vitamin-C and vitamin-E in combination gives the synergistic anti-oxidant action. The study results suggest that vitamin-C and vitamin-E affect liver regeneration by enhancing the functional role of hepatocytes functioning of several growth factors and cytokines in liver regeneration [35]. Vitamin B complex medicine is helpful in the cytological reformation of liver cells. Liver cellular regeneration is the complex process shown the ubiquitous expression of ALR in the liver and other parts also, Protein functions in the different ALR iso-formation which is emphasized by their differential subcellular localization. Different ALR isoform not only require the protein but they formed through selective mRNA expression at different ATGs or as post translational modifications" products of the longest form (23 kDa). The last option for the best in acute cirrhosis is liver transplantation. The herbal medicinal plants screened for phytochemical constituent act as a resource for the drugs as hepatoprotective medicine not only in treatment but also as a health source to maintain the health status. ALR gene expression will aid in the better understanding of ALR different functions and facilitate its possible future use as a therapy option [36].

9. References

1. Bernal W, Auzinger G, Dhawan A, Wendon J. Acute liver failure. The Lancet 2010; 376(9736):190-201.
2. Victor JN, John MDR. Current Concepts: Drug-Related Hepatotoxicity. N Engl J Med 2006; 354:731-739.
3. William M. Lee. Medical Progress: Drug-Induced Hepatotoxicity. N Engl J Med 2003; 349:474-485.
4. Girish C, Koner BC, Jayanthi S, Rao KR, Rajesh B, Pradhan SC. Hepatoprotective activity of six polyherbal formulations in CCl 4-induced liver toxicity in mice. Indian J Exp Biol 2009; 47(4):257-263.
5. Stuppner H, Kählig H, Seligmann O, Wagner H. Minor cucurbitacin glycosides from Picrorhiza kurrooa. Phytochem 1990; 29(5):1633-1637.
6. Choi MK, Kim HG, Han JM, Lee JS, Lee JS, Chung SH, Son CG. Hepatoprotective effect of Terminalia chebula against t-BHP-induced acute liver injury in C57/BL6 mice. Evid Complement Alternat Med 2015; 2015:1-8.
7. Meera R, Devi P, Kameswari B, Madhumitha B, Merlin NJ. Antioxidant and hepatoprotective activities of Ocimum basilicum Linn. and Trigonella foenum-graecum Linn. against H2O2 and CCL4 induced hepatotoxicity in goat liver. Indian J Exp Biol 2009; 47(7):584- 590.
8. Kiruthiga PV, Shafreen RB, Pandian SK, Arun S, Govindu S, Devi KP. Protective effect of silymarin on erythrocyte haemolysate against benzo(a)pyrene and exogenous reactive oxygen species (H2O2) induced oxidative stress. Chemosphere 2007; 68(8):1511–1518.
9. Papetti A, Daglia M, Gazzani G. Anti- and pro-oxidant activity of water soluble compounds in cichorium intybus var. silvestre (treviso red chicory) J Pharm Biomed Anal 2002; 30(4):939–945.
10. Böhm F, Köhler UA, Speicher T, Werner S. Regulation of liver regeneration by growth factors and cytokines. EMBO Mol Med 2010; 2(8):294-305.
11. Mortezaee K, Khanlarkhani N. Melatonin application in targeting oxidative- induced liver injuries: A review. J Cell Physiol 2018; 233(5):4015-4032.

12. Ghosh T, Maity TK, Das M, Bose A, Dash DK. In vitro antioxidant and hepatoprotective activity of ethanolic extract of Bacopa monnieri Linn. aerial parts. Iran J Pharmacol Therapeut 2007; 6:77-85.
13. S. Sengottuvellu, S. Duraisami, J. Nandhankumar, R. Duraisami M. Vasudevan. Hepatoprotective Activity of *Camellia sinensis* and its Possible Mechanism of Action. Iran J Pharmacol Therapeut 2008; 7:9-14.
14. Amin ZA, Bilgen M, Alshawsh MA, Ali HM, Hadi AH, Abdulla MA. Protective role of Phyllanthus niruri extract against thioacetamide-induced liver cirrhosis in rat model. Evid Complement Alternat Med 2012; 2012:1-9.
15. Mahmood L. The metabolic processes of folic acid and Vitamin B12 deficiency. J Health Res Rev 2014; 1(1):5-9.
16. Khanna AK, Rizvi F, Chander R. Lipid lowering activity of Phyllanthus niruri in hyperlipemic rats. J Ethnopharmacol 2002; 82:19-22.
17. Fakurazi S, Nanthini U, Hairuszah I. Hepatoprotective and anti-oxidant action of *Moringa Oleifera lam.*against acetaminophen induced hepatotxicity in rats. Int J Pharmacol 2008:4(4):270-275.
18. Girish C, Koner BC, Jayanthi S, Rao KR, Rajesh B, Pradhan SC. Hepatoprotective activity of six polyherbal formulations in paracetamol induced liver toxicity in mice. Indian J Med Res 2009; 129(5):569-578.
19. Grant A, Waugh A, Wilson JW. Ross and Wilson Anatomy and Physiology in Health and Illness. London: Churchill Livingstone Elsevier Science, 2001.
20. Guyton A, Hall JE. Textbook of Medical Physiology. Philadelphia: The Curtis Center, 2000.
21. Penman I. Davidson's Principle and Practice of Medicine. London: Churchill Livingstone Elsevier Science, 1999.
22. Mohan H. Textbook of Pathology. New Delhi: Jaypee brothers Medical Publishers (P) Ltd, 2000.
23. Kumar, Cotran, Saunders. Robbin's Basic Pathology. Philadelphia: The Curtis Center, 2004.
24. Damjanov I. Histopathology A Color Atlas and Text Book. Baltimore: Williams and Wilkins, 1996.
25. Gennavo AR, Remington. The science and practice of pharmacy. Philadelphia: Lipincott Williams and Wilkins, 2000.
26. Zimmerman HJ, Ishak KG. Hepatotoxin injury due to drugs and toxins. London Churchill Livingstone, 2002.
27. Kurma SR, Mishra SH. "Studies on Curculigo orchoides gaertn for Anti-inflammatory and Hepatoprotective Activities". Indian Drugs 1995; 29(6):20-22.
28. Handa SS, Sharma A, Chakraborthi KK. Natural products and plants as liver protecting agents. Fitoterapia 1986:7(5):307-351.
29. Ansari RA, Tripathi SC,Patnaik GK, Dhawan BN. Antihepatotoxic properties of picroliv: an active fraction from rhizomes of *Picrorhiza kurrooa*. J Ethnopharmacol 1991; 34(1):61-68.
30. Murthi MS, Srinivasan M. Hepatoprotective effect of *Tephrosia purpurea* in experimental animals. Ind J Pharmacol 1993; 25:34-36.
31. Mitra SK, venkataranganna MV, Sundaram R, Gopumadhavan S. Protective effects of HD-03 A herbal formulation against various hepatotoxic agents in rats. J Ethnopharmacol 1998; 63:181-186.
32. Dahiru D, Obidoa O. Pretreatment of albino rats with aqueous leaf extract of *Ziziphus mauritiana* protects against alcohol induced liver damage. Trop J Pharm Res 2007; 6(2):705-710.
33. García Rodríguez LA, Wallander MA, Stricker BH. The risk of acute liver injury associated with cimetidine and other acid- suppressing anti- ulcer drugs. British J Clin Pharmacol 1997; 43(2):183-188.
34. Shakil NA, Kumar J, Pandey RK, Saxena DB. Nematicidal prenylated flavanones from Phyllanthus niruri. Phytochem 2008; 69(3):759-64.
35. Sara Ibrahima, Thomas S. Weissa. Augmenter of liver regeneration: Essential for growth and beyond. Cytokine Growth Factor Rev 2019; 45:65–80.
36. Hermann S, Hanspeter KH, Otto S, Hildebert W. Minor Cucurbitacin glycosides from picrorhiza kurrooa. Phytochem 1990; 29(5):1633-1637.