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Herbal alternatives for the treatment of hepatic disorders: An updated review

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ABSTRACT

The liver is an amazingly complex organ which virtually affects every physiological process of the body. The liver is the largest glandular organ in body, and has more function than any other organs. Hepatic disorders which stem from a stressful life style, inappropriate eating habits and lack of exercise have become one of the major causes of morbidity and mortality in human being. The acute hepatic symptoms may be cured by some general prevention such as avoidance of constipation and balance between intake quantity of protein and disaccharides in normal food. An alternative and a progressively increasing adaptation is the use of herbal extracts. Many of the plant based drugs show effective response in managing the hepatotoxicity and secondary symptoms of liver damage. While, the models used for conventional hepatotoxicity evaluation are still outdated, in the present review we have attempted to provide updated information of the molecular pathogenesis and aspects for the role of herbalpharmacotherapy in alleviation of hepatic ailments. Furthermore, we have attempted to summarize the critical findings on hepatoprotective herbs over a period of last 20 year. In this article different hepatotoxicity pharmacological model such as carbon tetra chloride, paracetamol and thiocetamide induced are studied for different plants drugs. In summary this article contains the entire elucidated concept for hepatotoxicity including its causes, pathogenesis and treatment of liver disease.

Indexing terms/Keywords: Hepatotoxicity; hepatoprotective herbs; hepatic injury; hepatic function test; Silybummarianum; Alliumsativum.

Academic Discipline And Sub-Disciplines

Pharmacology, Ethanopharmacology

SUBJECT CLASSIFICATION

Pharmacognosy and Ethanopharmacology , Hepatoprotective

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INTRODUCTION

Medicinal plants may serve as a vital source of potentially useful new compounds for the development of effective therapy to combat a variety of disease. Herbal medicine is used by about 80% of the world population primarily in the developing countries for primary health care. Ancient literatures also mention herbal therapy for age related diseases namely memory loss, osteoporosis, diabetic wounds, immune and liver disorder, etc. The Indian traditional medicine like Ayurveda, siddha and unani are predominantly based on the use of plant materials. Herbal drugs have gained importance and popularity in recent year because of their safety, efficacy and cost effectiveness (Agarwal, 2001). Recently, World Health Organization defined traditional medicine including herbal drugs as therapeutic practice that have been in existence, often for hundreds of years, before the development and spread of modern medicine and are still in use today(Handa, 1999). The association of medical plants with other plants in their habitat also influences their medicinal value in some cases. One of the most important and well documented uses of plant product is their use as medication. Hence, there is an even increasing need for the safe medication(Thyagarajan et al., 2002).

ROLE OF LIVER IN HUMAN PHYSIOLOGY

Liver is absolutely crucial to life. Because it is responsible for so many vital functions, when the liver is damaged, our health is affected. The liver can do 500 functions - that's some multitasking! This is one powerful organ, the one organ in the body that is capable of regenerating itself. There is no organ that is more important to healthy metabolism than the liver- in many ways, it is as central to metabolisms the heart is to the circulation of blood. The liver plays a critical role in four key areas of metabolism: fuel management, nitrogen excretion, the regulation water distribution between the blood & tissues, and the detoxification of foreign substances. It also produces prothrombin and fibrinogen which helps in blood clotting and heparin, a mucopolysaccharide, sulphuric acid and ester that helps keeps blood from clotting within the circulatory system. The liver converts sugar in to glycogen. Liver play a vital role for disease free life. Because of (1) Storage of vitamins, minerals, and sugars.(2) Filter your blood and remove harmful substances. (3) Store extra blood for emergencies. Being prepared can be a lifesaver! (4) It keeps the electrolyte balance maintained. Electrolytes like calcium and potassium help the heart to keep beating! (5) It helps to utilize fat-soluble vitamins like A (for eyesight), D (helps calcium to absorb), E (good for wound healing), F (essential fatty acids for normal growth and behavior), and K (helps blood to clot). (6) It helps use or eliminates excess hormones. (7) It creates bile, which helps break down fats. (8) It helps to manage blood sugar - helping to keep blood sugar stable. Without the liver functioning correctly, it can lead to diabetes or hypoglycemia, or reactive hypoglycemia (highs and lows). (8) Processing digested food from the intestines. (9) Whatever wastes that the kidney does not remove from circulation, the liver removes from circulation. (10) Clearing bacterial infection and combating infections in general. An impaired liver means an impaired ability to fight infections. (11) Neutralizing toxins and drugs.

A few signs that the liver needs to be cleansed could be (if other things are not causing the symptoms)

If you experience any of the following symptoms, you may be experiencing autointoxication (a process whereby you are poisoned by substances produced by your own body as a result of inadequate digestion and elimination), (1) Breaking out in acne - which, of course is hard on the self-esteem. (2) Hair breakage. (3) Nightmares - bad dreams. (4) Insomnia. (5) Exhaustion. (6) Flu-like feelings. (7) Difficulty thinking or focusing. (8) Pain under right rib. (9) Blood sugar imbalance.

CAUSES OF LIVER DISORDERS

Liver diseases have become of the major cause of morbidity and mortality in human being. Among the many diseases that can affect the liver the most common is viral hepatitis (Figure 1). Hepatitis can be caused by drugs, viruses, bacteria and parasites like amoebias and giardiasis. The use of natural remedies for the treatment of liver diseases has a long history and medicinal plants and their derivatives are still used all over the world in the form or the older for this purpose (Nadeem et al., 1997). The liver protective plants contain wide variety of chemical constituent phenols, coumarins, monoterpenes, carotinoids, glycoside and polyphones. The main cause of hepatotoxicity is yet unknown. It appears to involve two pathways- direct hepatotoxicity and adverse immune reaction(Lewis & Elvin-Lewis, 1977). The most common hepatotoxicity induced by the bio activation of drugs to the active metabolites, which have ability to react interact with cellular macromolecules such as proteins, lipids and nucleic acid leading to protein dysfunction, lipid peroxidation, DNA damage and oxidative stress (Figure 2).

The reactive metabolites may induce disruption of ionic gradients and intracellular calcium stores, resulting in mitochondrial dysfunction and loss of energy production. Its dysfunction release excessive amount of oxidants which in turn causes injury to hepatic cells. Activation of some enzymes in the cytochrome P-450 system such as CYP2E1 also leads to oxidative stress (Figure 3). Injury to hepatocyte and bile duct cells lead to accumulation of bile acid inside the liver. This promotes further liver damage. This impairment of cellular function can culminate in cell death and possible liver failure. Thus it is the delicate balance of inflammatory and hepatoprotective mediators produce after the activation of the innate system that determines an individual's susceptibility and adaptation to hepatic injury (Lynch & Price, 2007).

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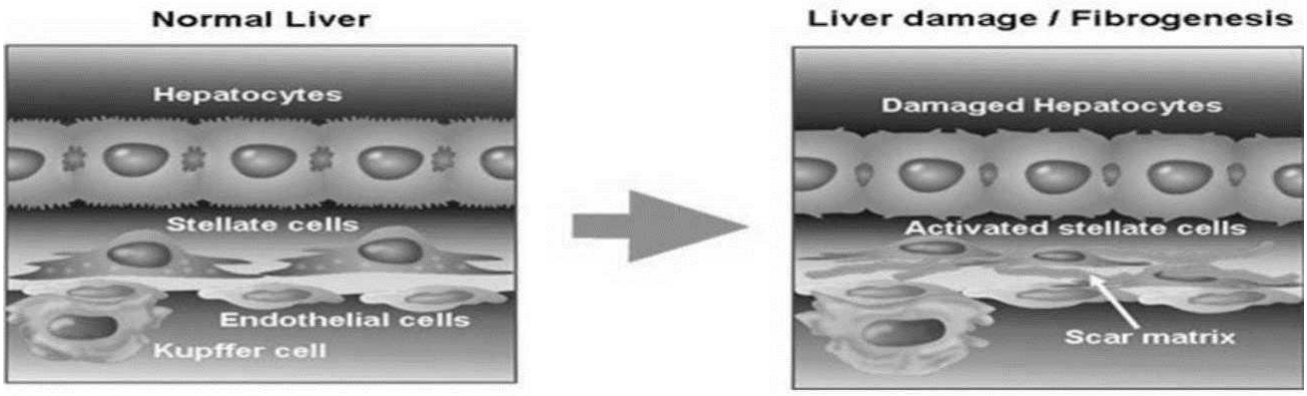

Fig 1: Difference between normal liver cells and infected liver cells

Fig 2: Route of hepatic injury

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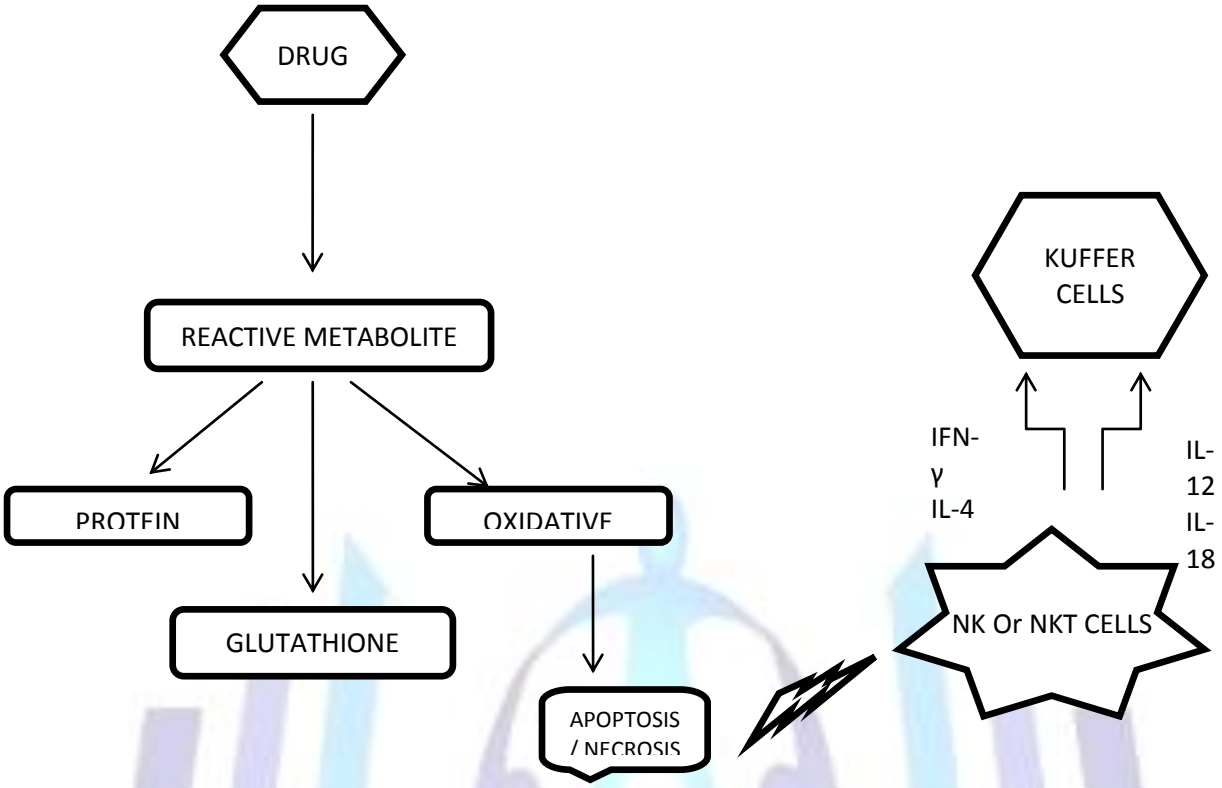

Fig 3: Mechanism of liver injury

MANAGEMENT OF HEPATIC ENCEPHALOPATHY

Some most common factors which helps to manage the hepatic injury.

- Avoid constipation
- Avoid other precipitating factors
- Maintain adequate protein and energy intakes
- Non absorbable disaccharides- lactulose 20-40 ml daily.

Pharmacological evaluation of hepatoprotective plants

To investigate hepatotoxic substances, it is customary to subject animals to a range of toxic substances. These include carbon tetrachloride, alpha amanitine and phalloidin, Paracetamol, liquid paraffin, thiocetamideetc, which induce animals liver damage, and changes in serum ALT and AST and further histological observation are evaluated.

In vivo models-The various in vivo models are studied for the evaluation of hepatic protective drugs. The models are listed below-

Paracetamol induced hepatotoxicity- The method of acetaminophen induced acute hepatotoxicity can be used most widely. Albino Rats are used for the pharmacological evaluation of the test drug. The standard and test drug of various concentrations is given to the rats and different parameters like evaluation of serum bilirubin, SGPT, SGOT are tested.

Carbon tetrachloride induced hepatotoxicity–The carbon tetrachloride is used for the induced hepatotoxicity in to the animal. The animal shows fatty changes, gross necrosis, broad inflammation of the lymphocytes and kupffer cells around the central vein. SGPT, SGOT, ALP serum bilirubin are most sensitive test which are consider as a index to estimate the liver disease.

Thioaetamide induced hepatotoxicity–Adult female wistar rats weighting 180-200 g are kept in wired bottomed cages at control temperature with 12 h. The thiocetamide and test group received the saline from the rats and evaluated different parameters like SGPT, SGOT, ALP and AST.

Alcohol and carbon tetra chloride induced hepatotoxicity

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Carbon tetra chloride and liquid paraffin induced hepatotoxicity(Pulok, 2012)

In vitro models- Developed in the past years. Next to their use in drug development, they can also be applied to study environmental toxins and their hepatotoxicity. The 3 main approaches are ex vivo isolated and perfused organ models, precision-cut liver slice and cell culture models. Although the advantage of whole organ perfusions is based on the assessment of physiologic parameters such as bile production and morphologic parameters such as tissue histology, cell culture models can be efficiently used to assess cellular metabolism, cytotoxicity and genotoxicity. The advantage of precision-cut liver slices is based on the juxtaposition of cellular assays and tissue morphology.

Hepatoprotective Herbs

***Silybummarianum*-** Milk thistle (*Silybummarianum*) has a long and important history in herbal medicine dating back over 2,000 years in European herbal traditions. The root, leaf and steam have medicinal use. But flavonolignans most widely used now a days. The extracts were injected to the rats, at a dose of 25 mg kg-1 body weight together with thioacetamide at a dose of 50 mg kg body weight. Significant decrease in the activity of aminotransferases, alkaline phosphatase and bilirubin was observed in the groups treated with extracts and compared with the group that was treated only with thioacetamide(Madani, Talebolhosseini, Asgary, & Naderi, 2008).

Other plants dugs which are reported as hepatoprotective is given below-

Table 1: List of various hepatoprotective herbs with proper biological screening metthod

S. No.	Plant name	Family	Part used	Model used	Animal used	Tested parameters	Dose/ route of administration	Reference
1.	*Andrograp hispanicul ata*	Acanthace ae	Leaves	Paracetam ol -induced	Healthy adult male Wistar albino rats (weighing between 120-250g)	AST, ALT, GGT, ALP, LDH and bilirubin	500 mg/kg b.w, p.o.	(Rajalaksh mi, Arul Jothi, Venkatesa n, & Jegathees an, 2012)
2.	*Allium sativum*	Liliaceae	Bulb	Isoniazid induced	Wistar albino rats	ALT, AST, ALP and Total Bilirubin	0.25 g/kg/day, oral route	(Chattopad hyay & Bandyopa dhyay, 2005; Ilyas, Sadiq, & Jehangir, 2011)
3.	*Azadiracht aindica*	Meliaceae	Aerial parts	Paracetam ol induced	Male albino Wistar rats (100-150 g; 4-6 weeks old)	GST, GPX, SOD	500 mg/kg, p.o.	(Chattopad hyay & Bandyopa dhyay, 2005; Jeong et al., 2002)
4.	*Boerrhavia diffusa*	Nyctaginac eae	Whole plant	Thioaceta mide	Albino rat	GOT, GPT, ACP and ALP ,TG and ALT	100mg/gm bw	(Aghel, Rashidi, & Mombeini, 2010; Rawat, Mehrotra, Tripathi, & Shome,

								1997)
5.	*Curcuma longa*	Zingiberaceae	Rhizome	Paracetamol induced	Male albino Wistar rats (100-150 g)	ALT, AST, ALP	600mg/kg oral route	(Kumar, Ahuja, & Sharma, 2008; Somchit, Sulaiman, Noratunlina, & Ahmad, 2002)
6.	*Wedeliacalendulaceae*	Asteraceae	Leaves	Thioacetamide induced	Albino rat	SGOT, SGPT, ALP LP, GSH	(100, 200 and 400mg/kg B.W.) oral route	(Haldar, Gupta, Mazumder, Kandar, & Manikandan, 2007)
7.	*Camellia sinensis*	Theaceae	Leaves	Chloroform indcued	Male albino rat	CAT, SOD, GSH	100mg/kg and 200 mg/kg	(Sengottuvelu, Duraisami, Nandhakumar, Duraisami, & Vasudevan, 2008)
8.	*Cappariss pinosa*	Capparidaceae	Leaves	Carbon tetra chloride induced	Male albino rat	ALT, AST	100mg/kg, oral route	(Aghel et al., 2010)
9.	*Cassia tora*	Leguminosae	Leaves	Galactosamine induced	Albino rats	ALT, AST, SGOT, SGPT, Bilirubin,	100 and 250mg/kg i.p.	(Rajan, Shanmugavalli, Sunitha, & Umashankar, 2009)
10.	*Cichoriumintybus*	Asteraceae	Leaves	Chlorpromazine induced	Adult albino rat	Leukocytes	300mg/kg	(Heibatollah, Reza, Izadpanah, & Sohailla, 2008)
11.	*Glycyrrhizaglabra*	Leguminosae	Leaves	Carbon tetra chloride induced	Male albino rat	ALT, GST, GSH, SOD	500 mg/kg, subcutaneous	(Jeong et al., 2002)
12.	*Ginkgo biloba*	Ginkgoaceae	Whole plant	Carbon tetra chloride induced	Male albino rat	ALT, AST, ALP	0.5 g/kg body weight per day, subcutaneous injection	(He et al., 2006; Shenoy, Somayaji, & Bairy, 2001)
13.	*Ocimum sanctum*	Labiateae	Leaves	Paracetamol and carbon tetra chloride	Albino rats (150–200 g)	Total serum protein, albumin globulin ratio, ALP, AST and ALT	100 mg/kg BW/day, p.o.	(Lahon & Das, 2011)

14.	*Phylanthus niruri*	Euphorbiaceae	Leaves	Carbon tetra chloride induced	Mice	SGOT	5 mg/kg body weight,orally&intraperitoneally	(Bhattacharjee & Sil, 2007)
15.	*Rheum emodi*	Polygonaceae	Root	Paracetamol induced	Albino rats (150–200 g)	ALT, AST, ALP, albumin and bilirubin (total and direct) levels	2 g/kg, orally	(Akhtar, Amin, Ahmad, & Alamgeer, 2009)
16.	*Taraxacu mofficinale*	Asteraceae	Whole plant	Glactosamine induced	Sprague-Dawley rats	Dandelion	3% DWE diet, i.p.	(Park, Park, Kim, & Song, 2008; A. Singh, Malhotra, & Subban, 2008)
17.	*Vitisvinifera*	Vitaceae	Leaves	Carbon tetra chloride induced	Male albino rat	ALT, AST	125 mg/kg dose (per os)	(Orhan, Orhan, Ergun, & Ergun, 2007)
18.	*Tephrosia purpurea*	Fabaceae	Roots & leaves	Galactosamine,carbon tetra chloride induced	Male albino rat	SGOT, SGPT, bilirubin level	500mg/kg, orally	(Bishayi, Roychowdhury, Ghosh, & Sengupta, 2002)
19.	*Tinosporacordifolia*	Menispermaceae	Whole plant	Carbon tetra chlorideinduced	Adult male albino rat	SGOT, SGPT and ALP	100mg/kg/d. i.p.	(Sree & Srinivasan, 1993)
20.	*Zingiberoffi cinale*	Zingiberaceae	Rhizome	Ferric chloride induced	Sprague Dawley rats (150-170 g)	ALP, SGPT, SGOT, ALT, AST	500 mg/kg, orally	(Atta et al., 2010)
21.	*Eclipta alba*	Composite	Leaves	Paracetamol, carbon tetra chloride induced	Albino wistar rats	sleep time ,zoxazolamine paralysis time, bromosulphaline clearance, serum transaminases and serum bilirubin	10-80 mg/kg, p.o.	(B. Singh, Saxena, Chandan, Agarwal, & Anand, 2001)
22.	*Foeniculumvulgare*	Umbelliferae	Fruit	Carbon tetra chloride induced	Sprague-Dawley rats weighing 180-200 g	serum aspartate aminotransferase, alanine aminotransferase, alkaline	0.3 ml/kg i.p.	(Hanefi et al., 2004)

						phosphatase		
23.	*Trigonellafoenumgraecum*	Leguminosae	Fruit	Thiobarbituric-acid induced	Albino wistar rats	ALT,AST serum bilirubin	200 mg kg^{-1} day^{-1}, orally	(Kaviarasan, Viswanathan, & Anuradha, 2007)
24.	*Ficuscaric a*	Moraceae	Leaves	Carbon tetrachloride induced	Albino wistar rats	ALT,AST serum bilirubin	500mg/kg	(Mohan, Pallavi, Kumar, Ramesh, & Venkatesh, 2007)
25.	*Annonasquamosal*	Annonaceae	Leaves	Isoniazid+rifampicin induced	Albino rats	Decreased ALT,AST,	300mg/kg b.w, i.p.	(Saleem, Christina, Chidambaranathan, Ravi, & Gauthaman, 2008)
26.	*Lepidiumsativum*	Brassicaceae	Leaves	Carbon tetrachloride	Albino wistar rats	AST, ALT, ALP levels and bilirubin	200 and 400 mg/kg body weight, i.p.	(Afaf, Abuelgasim, & Mohammed, 2008)
27.	*Sargassumpolycystum*	Sargassaceae	Leaves	Galctosamine induced	Wistar strain male albino rats	ALT,AST	125mg/kg b.w, orally	(Meena et al., 2008)
28.	*Prosthecheamichuacana*	Orchidaceae	Leaves	Carbon tetra chloride induced	Albino rats	Blood biochemical profile	200-600mg/kg b.w, orally	(Gutiérrez & Solís, 2009)
29.	*Phyllanthusamarus*	Euphorbiaceae	Leaves	Carbon tetra chloride induced	Albino rats	AST, ALT, SGOT	25, 50 and 75 mg/kg, p.o.	(Pramyothin, Ngamtin, Poungshompoo, & Chaichantipyuth, 2007)
30.	*Fumariaindica*	Fumariceae	Leaves	Paracetamol and carbon tetra chlorideinduced	Albino rats	Serum biochemical parameters	10–20 mg p.o	(Rao & Mishra, 1997)
31.	*Silybummarianum*	Asteraceae	Leaves	Thiocetamideinduced	Albino wistar rats	Aminotransferases, bilirubin, alkaline phosphates	25mg/kg b.w, p.o.	(Heibatollah et al., 2008)
32.	*Cassia roxburghii*	Caesalpiniaceae	Seeds	Carbon tetra chloride+ethanolinduced	Albino wistar rats	AST, ALT, SGOT	250-500mg/kg	(Arulkumaran et al., 2009)

33.	*Cocciniagrandis*	Cucurbetaceae	Leaves	Carbon tetra chloride induced	Albino wistar rats	ALT, AST, amino transferases	250mg/kg	(Vadivu et al., 2008)
34.	*Solanumnigrum*	Solanaceae	Fruits	Carbon tetra chloride induced	Male albino rats	AST, ALT, ALP and total bilirubin	250 mg/kg, p.o.	(Sultana, Perwaiz, Iqbal, & Athar, 1995)
35.	*Orthosiphonstamineus*	Laminaceae	Leaves	Paracetamol induced	Male albino rats	Decreased in level of ALT AST	200mg/kg	(Maheswari, Maryammal, & Venkatanarayanan, 2008)

(s.c- sub cutaneous i.p.-interaperitonial, b.w- body weight, AST- Aspartate Aminotransferases, ALT- Alanine Aminotransferases, ALP- Alkaline Phosphates, SGOT- Serum Glutamic Aminotransferases, SGPT- Serum Glutamic Phosphotransferases)

Table 2: List of various Hepatic functions tests with their interpretations(Kashaw, Nema, & Agarwal, 2011)

Hepatic function test parameters	**Abbreviations**	**Reference range**	**Interpretations**
Albumin	Albumin	3.5 to 5.3 g/dL	To assess severity of liver injury (HIV infection and malnutrition may confound this.)
Alkaline phosphatase	ALP	3.5 to 5.3 g/dL	To diagnose cholestasis and infiltrative disease x
Alanine transaminase	ALT	7 to 56 IU/L	To diagnoses liver dysfunction
Anti-mitochondrial antibody	AMA	< 0.1 units	To diagnose primary biliary cirrhosis
Aspartate transaminase	AST	6 to 40 IU/L	Elevated AST levels are not specific for liver damage, and AST has also been used as a cardiac marker
Bilirubin (unconjugated)	Bilirubin (unconjugated)	0.1 to 0.4 mg/dL	To assess for hemolysis
Bilirubin (total)	Bilirubin (total)	0.1 to 1.0 mg/dL	To diagnose jaundice and assess severity
Gamma glutamyltranspeptidase	GGT	0 to 42 IU/L	GGT is raised in chronic alcohol toxicity
Serum glutamic oxaloacetic transaminase	SGOT	5 to 40 IU/L	To diagnose hepatocellular disease and assess progression of disease
Serum glutamate pyruvate transaminase	SGPT	7 to 56 IU/L	ALT relatively lower than AST in persons with alcoholism

DISCUSSION

Hepatoprotective disorder is the most common disorder and affects normal physiology of liver. This review discusses the plant drugs which have shown significant result as the hepatoprotective agent even in some cases with good potency. There is an increasing demand by patient to use the natural product with hepatoprotective activity. Large number of herbal species has been used traditionally as a medicine against hepatotoxicity ailments. Many of them have been studied scientifically and proved to be beneficial for liver as a hepatoprotective. The success has been attained to isolate various single chemical entities responsible for hepatoprotective activity(Stickel & Schuppan, 2007). Most of the plant extract is water soluble so the achievement of successful bioavailability is tough task. To overcome these problems different kinds of targeted formulation have been developed. In this aspect phytosomes and liposomes have emerged as prospective tools for delivery of bioactive to hepatic tissues. The different kind of marketed formulation such as silyphosphytosomes, ginkgo liposomes, quercetinphytosomes are available in the market which achieve maximum bioavailability(Murray, 2008).

CONCLUSION

Plants have played a remarkable role in health care since the ancient time. traditionally plant based medicine exert a great deal of importance to people living in developing countries and also lead to discovery of new drugs. Herbal medicines make an enormous contribution to primary health development. In the recent days hepatotoxicity is a major cause for the human being so this review includes all the study of plants drug which gives significant response for the treatment of hepatotoxicity. The research of botanical medicines shows different result for the treatment of liver dysfunction. The different herbal remedies such as green tree, ginger, and curcumin are the well-known drugs for the treatment of acute liver toxicity.

In other way many hepatic trails are done by the scientist today and much research yet to be done, but list of these plants has an appreciable response for the treatment of viral hepatitis, cirrhosis of liver and liver toxicity. The single drug cannot be show significant response; the combination of two or more plant extract may prove very effective treatment of liver disorders caused by over drinking of alcohol, toxic elements and different viral infections.

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