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A Comparative Review on Medicinal Plants Used for the Liver Disorders as in Ayurved, Siddha and Unani [ASU] Systems of Medicine

Part 2 - Phytochemical and Pharmacological Aspects

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ABSTRACT: Liver disorders mostly represent a prolonged dysfunction associated with different routes of cellular and biological alterations due to variety of reasons. Present treatments are found to be of limited use. Indigenous systems of medicine Ayurved, Siddha and Unani are extensively used to provide relief in variety of liver diseases. The understanding of liver functions, its dysfunctions and treatments offered have been of research interests. A series of review papers have been published by the authors covering different aspects including classical, proprietary and This review paper- part II is the outcome of the systematic effort and analyses of hepatoprotective formulations and ingredients with the updated information on phytochemical and pharmacological- safety aspects. This strongly emphasizes on the role of ASU products and ingredients to treat chronic or severe liver diseases. These systems and scientific information on products and plants exhibit huge translational potentials to evolve new path to understand and develop new safe and effective therapeutic approaches and drugs to treat liver disorders.

KEY WORDS: Liver disorders, Ayurved, Siddha, Unani, Medicinal plants, pharmacology

Patented products. A summarized outcome on 25 potential medicinal plants out of 106 has been published as part I.

BACKGROUND

Worldwide the liver diseases are significant cause of morbidity and mortality. Multiple etiological factors are cause of liver dysfunction that can lead to complex conditions although the rates of progression and clinical course may be different [1].

Ayurved, Siddha and *Unani* [ASU] are indigenous systems of medicine of India that provide descriptions of different types of liver diseases and offer therapeutic approaches, products, and ingredients of natural origin to treat them. Hundreds of liver products based on these systems are prescribed by physicians and used as remedies by people.

A series of reviews undertaken by the *Bhatt et al* provide major information about hepatoprotective herbal drugs used in ASU traditional medicine for the treatment of liver diseases [2-7].

METHODOLOGY

In a recent review, the ccontextual and clinical aspects of of 106 plants used singly or in combinations were scrutinized to prepare a priority list of 25 plants from ASU systems for treatment of liver disorders [8-19].

This review is based on phytoconstituents and preclinical data of medicinal plants used in liver disorders obtained through updated Google and PubMed searches to help to select high potential ingredients or their combinations.

LIVER AND LIVER DISORDERS IN ASU SYSTEMS][20-24]

The significance of the liver in the context of blood-fluid, which embodies one of the main humoral or functional systems of human biology, explicitly explained in the ASU systems. Any functional disturbance of the humoural system or the temperament may develop into various types of liver disorders and on the other hand, any impairment of liver function can affect one or more of the body functions. These pathological conditions vary in disposition and are a result due to weakened hepatic activity, dullness, inflammation, obstruction, trauma and such others.

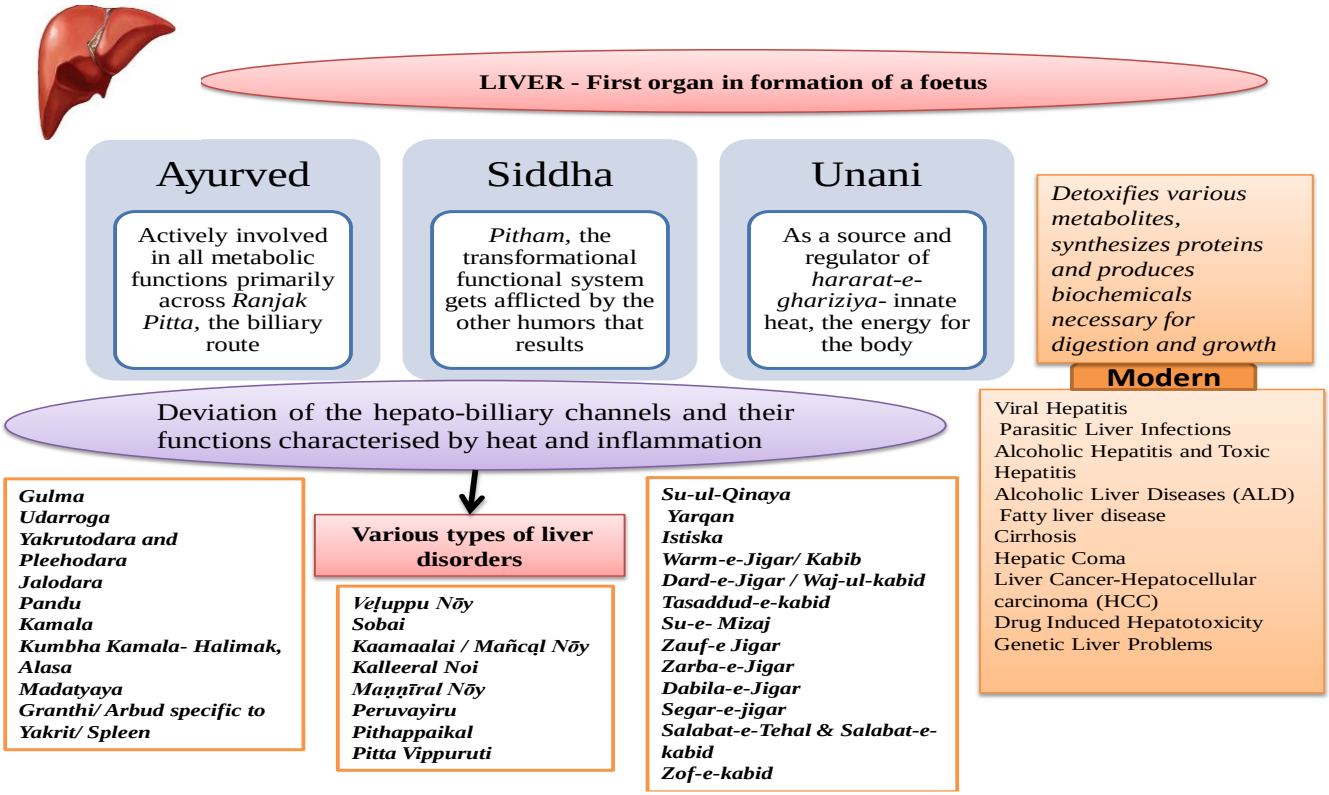

Fig 1- Summarize the Liver concept and liver diseases in ASU system of medicine

HIGH POTENTIAL MEDICINAL PLANTS

The potential **twenty-five** plants were screened and scrutinized based on published literature for scientific assessment of phytoconstituents and pre-clinical activities related hepatic functions listed in figure 2.

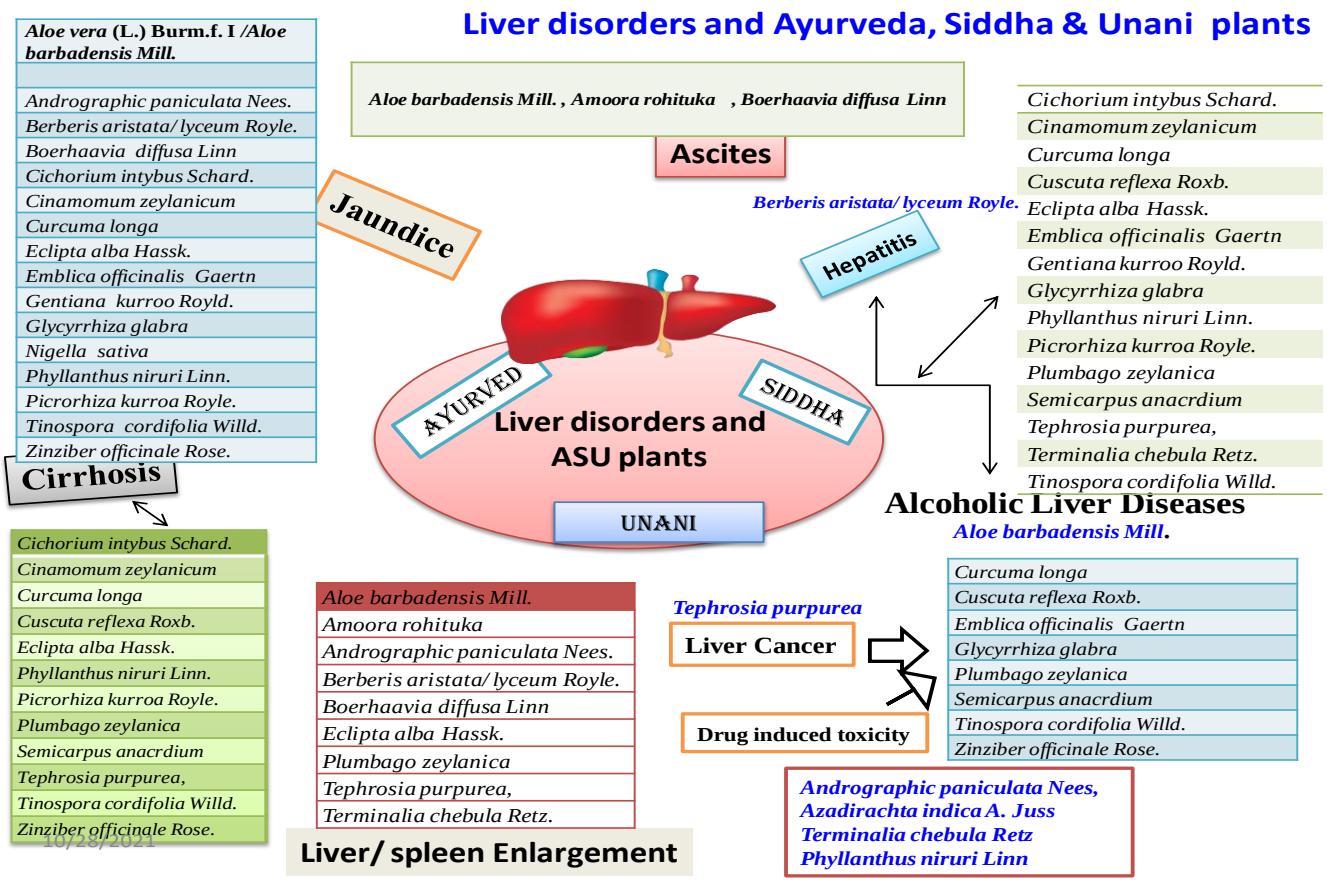

Figure 2: High Potential Medicinal Plants from ASU Systems for Liver Disorders

RESEARCH SIGNIFICANCE OF PHARMACOLOGICAL– PRECLINICAL AND SAFETY STUDIES

Aloe vera (L.) Burm.f. I /*Aloe barbadensis Mill (Liliaceae)*

Aloe, amongst one of the most well-known home remedy plant is used in ASU traditional systems of medicine for improving liver function by stimulating release of the bile. It contains Phenolic, Glycosides, Anthrones, Barbaloin, Aloe-emodin 12 anthraquinones.

Aloe *juice* has ameliorative effect in malathion induced hepatotoxicity in rabbits [25]. Hepatoprotective effect of the plant (stem) exhibited in *ethanol* and *aqueous extracts* in paracetamol induced liver damage [26], while petroleum ether, chloroform and methanol extracts in CCL_4 induced hepatotoxicity [27]. *Polysaccharides AVGP* in chronic alcohol feeding mice regulated hepatic expression of lipolytic genes (AMPK-α2 and PPAR-α), accelerated lipolysis and inhibited inflammatory response [28].

Whole leaf extract showed carcinogenic activity in rats, as a possible human carcinogen (Group 2B); a dose-dependent decrease in the viability in HeLa and HepG2 cells. Cytotoxicity and genotoxicity study of *whole extract* showed a positive response at lower concentrations than the decolorized extract in the mouse lymphoma assay (MLA). Reproductive toxicity - sperm damage, haematological changes, inflammation, mortality was observed after a chronic oral ingestion of 100 mg/kg *extract* per day, for 3 months [29].

Amoora rohituka (Roxb.) Wight&Arn./Tecoma undulata (Sm.) G.Don (Bignoniaceae)

Bark of *Rohitak* having blood purifying and cholagogue properties. It contains tecomin (veratroyl β-D-glucoside), n-triacontane, n-heptacosane, n-nonacosane, n-triacontanol, n-octacosanol; β-sitosterol. Its hepatoprotective activity observed in the *ethanolic extract of bark* in paracetamol induced hepatic damage [30], *methanol extract* of leaves in alcohol-induced hepatotoxicity in rats [31]. It prevented changes in metabolic

enzyme concentrations as well as diminished the destruction of liver cell architecture initiated by administration of $CC1_4$[32].

Andrographis paniculata Nees (Acanthaceae)

The king of bitters has strong liver stimulating activity to expel out excess bile, *pitta* from the body. It helps regulating hepatic function by reducing inflammatory biological factors. 55 *ent*-labdane diterpenoids, 30 flavonoids, 8 quinic acids, 4 xanthones, and 5 rare noriridoids are present in the plants.

The *aqueous extract* reduces CCl_4, paracetamol induced hepatotoxicity [33], prevents liver damage [34], antioxidant effect [35]. *Intra-peritoneal* in the albino rats the *extract* has choleretic effect with qualitative changes and increase in the bile secretion [36]. In galactosamine and paracetamol intoxication, it helps normalize the biochemical parameters [37-38], hepatic microsomal drug metabolizing enzymes [39-40]. The diterpenes *andrographolide* (I), *andrographiside* (II) and *neoandrographolide* (III) exhibited protective effects on CCl_4 or tert-butylhydroperoxide intoxication hepatotoxicity in mice [41].

No acute or sub acute toxicity was observed in LD – 50 studies with andrographolide and derivatives [42]**.**

Azadirachta indica, A. Juss (Meliaceae)

The world famous Margosa tree for its antipollution attributes amongst many known properties is recognized for its anti-parasitic, healing, and hepato-protective effects where its anti-inflammatory activity regulates impaired levels of liver enzymes. The most important active constituents are azadirachtin, nimbolinin, nimbin, nimbidin, nimbidol, sodium nimbinate, gedunin, salannin, and quercetin.

Healing potential of the powder of Neem *leaves* on liver parenchyma with regeneration of liver cells has been studied in CCl_4 induced hepatotoxicity [44]. *Aqueous leaf extract* is useful in prevention and reversal of the hepatotoxic damage due to antitubercular drugs [45] and has shown hepatoprotective activity in paracetamol induced hepato-toxicity in albino rats [46-47].

Ethanolic, *methanolic*, *aqueous leaf extracts* have shown hepatoprotective effects in CCl_4 induced hepatotoxicity [48-49] and the *methanolic extract* alleviates cisplatin-induced damage and oxidative stress in liver [50].

Azadirachtin-A, *Nimbolide* reduced hepatocellular necrosis in CCl_4 induced hepatotoxicity and has antioxidant effect [51]. Oral administration of *water extracts of leaves and seeds* exhibited dose related toxicity-with decrease in death percentage from 100 % to 33 % in rats and rabbits; variable solvents and methods of preparation could affect the levels of toxicity [52].

Nimbolide and *nimbic acid* are ***toxic*** to mice only when given i.p. and i.v. but they are less toxic to rats and hamsters by the oral route. It observed dose-related pharmacotoxicity symptoms [possible dysfunctions in kidney (tubular necrosis), small intestine (hemorrhagic necrosis), pancreas (acinar cell necrosis) and liver (mild fatty infiltration and focal necrosis [53]. Neem *oil* which is regularly used did not have any toxicity in 90-day sub chronic toxicity studies as in serum biochemistry, organ weight and histopathology [54-55].

Berberis aristate DC. (Berberidaceae)

A strong astringent Berberis plant used effectively in treating anorexia and dysentery is a hepato-stimulant having cholagogue effect. It exhibits suppressing action on drug metabolizing enzymes and improves the functional recovery of beta cells. The plant contains barberine, oxyberberine, berbamine, aromoline, karachine, palmatine, oxyacanthine and taxilamine.

The hepatoprotective effects of its *crude powder* and *methanolic extract* are observed in paracetamol induced hepato-toxicity [56], the *fruit extract* in paracetamol-induced liver damage[57].

Berberine hydrochloride in Hepg2 Cancer cell exhibited regulation of prostaglandin E2 (PGE2) signalling pathway line via PGE2 and Cox2 inhibition [58].

Berberine showed antioxidant-hepatoprotective activity in CCl_4 induced hepatotoxicity [59], and in HFD - high fatty diet - induced rat model where methylation of the MTTP - microsomal triglyceride transfer protein - helped alleviate fatty liver[60].

Powdered root, extract and *pure berberine* showed ***sub-acute toxicity*** on rat, rabbit and mice. The sub-acute concentrations of *berberine* lead to altered liver function, gastric troubles, hepato-hemato-toxicity, hemorrhagic inflammatory consequences, damage to immune cells and induced apoptosis. The in vivo and in vitro studies have reported that *sanguinarine* may induce apoptosis and adversely influence the embryonic development (both in the pre-implantation and post-implantation conditions) of mouse [61].

Boerhavia diffusa, Linn.(Nyctaginaceae)

Punarnava having large quantity of *nitrate content* has strong diuretic and anti-inflammatory activity and is frequently used in cirrhosis and ascites with advanced structural changes to reduce the functional liver burden. It contains b-Sitosterol, a-2-sitosterol, palmitic acid, tetracosanoic, hexacosonoic, stearic, arachidic acid, urosilic acid, Hentriacontane, b-Ecdysone, triacontanol etc.

Aqueous extract has shown antioxidant and hepatoprotective effects in acetaminophen, CCl_4 [62], paracetamol [63] and ethanol induced hepatotoxicity [64-65]. It has shown increase in lipid peroxides further increasing in activities of the superoxide dismutase, catalase, glutathione peroxidase and glutathione-S-transferase and reduced glutathione levels [67]. Its *hydroalcoholic extract* showed hepatoprotective activity in d-galactosamine induced hepatotoxicity [68].

Aqueous extract of leaves in sub-chronic toxicity studies on liver enzymes and haematological parameters was observed to be non-toxic [69] and in teratogenic studies no foetal anomaly were detected with its *ethanol extract* [70].

Cichorium intybus* L. *(Compositae)

Cichori plant is traditionally used in the treatment of almost all kinds of liver disorders like sluggish liver, enlargement of spleen, billiary stasis (stoppage of bile) and jaundice. It's cooling effect increases secretion of bile by reducing inflammation, remove obstruction, and helps in stomach pain and obesity. Inulin, coumarins, tannins, monomeric flavonoids, sesquiterpene lactones are some of the major phyto-compounds.

Hepatoprotective effects of *aqueous and alcoholic extracts* were observed in acetaminophen and CCL_4 induced liver damage in mice with decrease in the levels of increased hepatic enzymes [71-76]. Similarly anti-hepatotoxic effects with decrease in the hepatic enzyme levels were found with the *root and root callus extracts* in CCL_4 induced liver damage in rats [77].

Cichotyboside and its *ethanol extract* also improved liver enzyme levels in CCl_4 induced hepatotoxicity[78-79]. Phenolic acid-rich *seed extract* helped in restoration of normal levels of corresponding proteins in oleic acid-induced non-alcoholic fatty liver disease (NAFLD)/steatohepatitis (NASH) through modulation of PPAR-alpha and SREBP-1hepatic steatosis in vitro and in vivo –to up-regulate the expression of SREBP-1c and PPAR-α genes[80].

There is a slight potential for sensitization via skin contact with the drug [81].

Cinnamomum zeylanicum, Blume (Lauraceae)

Essential oils of cinnamon bark and leaf are widely used in food flavours, cosmetics and pharmaceuticals. E)-Cinnamaldehyde is the main component of cinnamon bark oil and eugenol the main component of the leaf oil.

Cinnamon bark extract and Oil Cinnamaldehyde have shown antioxidant and hepatoprotective activity in CCL_4 [82]and paracetamol induced hepatotoxicity[83].
Cinnamon and its main constituents ameliorate the toxicity in liver, kidney, blood, brain, embryo, reproductive system, heart, spleen through antioxidant effects, modulation of CK-MB, LDH, TNF-α, IL-6, mitogen-activated protein kinase (MAPK), and nuclear factor-κB (NF-κB) signalling pathways in vitro and animal studies on the protective effects against natural and chemical toxins[84].

Curcuma longa, L.* (*Zingiberaceae)
Golden spice of India has been used as a household remedy for various diseases, including biliary disorders. Turmeric contains curcuminoids (mixture of curcumin, demethoxycurcumin and bisdemethoxycurcumin). *Aqueous extract* of Turmeric has shown antioxidant-hepatoprotective activity in bleomycin-induced & ethanol-induced hepatotoxicity [85-86], *ethanol extract* in paracetamol induced toxicity [87].
Curcumin has shown variety of hepatoprotective in CCL_4 and lead induced hepatotoxicity[88], antioxidant activity[89], and its anti-inflammatory effect helped prevent the progression of irreversible liver dysfunction in dimethylnitrosamine (DMN) induced liver cirrhosis in rat model[87,90]. *Curcumin* exhibited enhanced hepatoprotective effects inhigh fat diet (HFD) NAFLD rat model [91] and billiary duct ligation (BDL) and also in marine model of non-alcoholic steatohepatitis methionine and choline deficient diet [MCD] with prevention of accelerating of oxidative associated liver diseases[92-95].
No adverse effect level (*NOAEL*) was observed for reproductive toxicity of *curcumin*, fed in the diet for two successive generations [96-97].
Curcumin in wistar rats did not show significant effect on the incidence of micro nucleated polychromatic erythrocytes, structural and numerical aberrations in bone-marrow chromosomes, pregnancy rate, and number of live and dead embryos, total implants and mutagenic index. No toxic effects were stated at doses of 3.5 g/kg given for 3 months in rats, dogs, and monkeys. The use of curcumin in humans by oral administration observed that 1.5 g of turmeric powder per day (about 150 mg of curcumin, average consumption in India) did not exhibit any side effects in humans [98].
Synthetic Curcumin did not show any mortality or 'No adverse effect level[*NOAEL*]', toxic effect or genotoxicity in 90-day repeated-dose at daily doses of 250, 500, or 1000 mg/kg body weight/day, administered by gavages in a split dose and repeated-dose[99].

Cuscuta reflexa* Roxb. (*Cuscutaceae)
C. reflexa contains cuscutin, amarbelin, β-sitosterol, stigmasterol, kaempferol, dulcitol, myricetin, quercetin, coumarin and oleanolic acid and has anti-tumor, anti-oxidant and anti-inflammatory activities.
Alcoholic extract of stem, whole plant showed hepatoprotective activities in paracetamol, carbon tetrachloride, ethanol induced hepatotoxic rat models [100-101]. The hepatoprotective effects were observed in *chloroform and ethanol ethanolic extract* in paracetamol and *alcoholic and aqueous extracts* of *stem* in thioacetamide induced liver damage in rats [102-103].

Eclipta alba f. prostrata (L.) Hassk.(Asteraceae)
Eclipta leaves are most commonly used in variety of liver disorders in all the three systems. A broad range of chemical components including alkaloids, alkenynes, cardiac glycosides, steroids, triterpenes, phytosterol, flavonoids, coumestans, glycosides, triterpinoids, saponins have been extracted from the plant.

Fresh powder, aqueous, hydroalcoholic and alcoholic extracts of leaves have repetitively shown hepatoprotective effects in CCL_4[104-108], alcohol[109] and paracetamol[110-112], induced acute or chronic liver damage in rats and anti-hepatotoxic activity in various hepatotoxins, aflatoxin induced acute hepatitis[113-115] by restoration of Na+K+ATpase activity and regulating hepatic microsomal drug metabolising enzymes. Also, *methanol extract of leaves* and *chloroform extract of roots* normalized serum GOT, GPT, ALP, and bilirubin levels in CCL_4 induced hepatotoxicity [116].

Coumestans (wedelolactone and dimethyl wedelolactone exhibited anti-hepatotoxic stimulatory effect on liver cell regeneration in assays employing CCl_4, GalN and phalloidin-cytotoxicity in rats [117].
Wedelolactone, luteolin, and *apigenin* also exhibited dose-dependent inhibition of HCV inhibitory activity by replication in vitro and anti-HCV (hepatitis C virus) in the cell culture system [118].

Emblica officinalis Gaertn

Emblica officinalis Gaertn or *Phyllanthus emblica Linn*, Indian gooseberry is one of the most important medicine, dietary and one of the ingredients of '*Triphala'* (combination of three fruits) that is most commonly used for a wide range of cathartic effects.
Amla fruit contains higher quantity of polyphenols like gallic acid, ellagic acid, different tannins, minerals, vitamins, amino acids, fixed oils, rutin and quercetin.
Scientific studies have shown that *Amalaki* is effective in preventing/ameliorating the toxic effects of hepatotoxic agents like ethanol, paracetamol, carbon tetrachloride, heavy metals, ochratoxins, hexachlorocyclohexane, antitubercular drugs and hepatotoxicity resulting from iron overload. It has beneficial effects on liver function, hyperlipidemia and metabolic syndrome [119].

Fruit extract has range of antioxidant and hepatoprotective effects as observed in alcohol induced hepatotoxicity in rats[120-121], arsenic induced hepatopathy in adult Swiss albino mice[122], chronic and preventive, pre-fibrogenesis of liver cells, with CCl_4 and thioacetamide induced liver damage[123-125]. Further *pre-treatment with seven consecutive* days inhibited hepatotoxicity in CCl_4 induced toxicity in wistar rats [126].
50% hydro-alcoholic extract of the fruit expressed stabilizing, antioxidative and cytochrome (CYP) 2E1 inhibitory effects in anti-tubercular drugs-induced hepatotoxicity [127]. In paracetamol and CCl_4 induced hepatotoxicity the *tannins, flavonoids, terpenoids, alkaloids of fruits* showed offset of necrosis with appearance of normal hepatocytes, and consequent appearance of leucocytes[128-129].

Amla supplementation counteracts NDEA induced liver injury via its antioxidant, anti-inflammation, anti-apoptosis, and anti-autophagy properties [130]. Its extract significantly inhibited hepato-carcinogenecity induced by NDEA in a dose dependent manner [131].

Glycyrrhiza glabra L. (Fabaceae)

World over the liquorice is a known home remedy including liver ailments like non- alcoholic fatty liver. Its extract reduces the concentration of ALT and AST, indicating its beneficial effect on the liver functions. Liquorice roots contain more than 20 triterpenoids and nearly 300 flavonoids. Glycyrrhizin and glycyrrhetinic acid are the main components.
Aqueous, hydro-methanolic and ethanol extracts of liquorice have variably shown hepatoprotective effects in CCl_4-induced hepatotoxicity, oxidative and in-vitro hepatocyte damage in rats[132-135] and ameliorating liver functions as well as restoring hepatic tissue in acute liver diseases[136]. *Methanol extract of roots* exhibited

glucuronidation in rat metabolism of acetaminophen in male Sprague-Dawley rats with increased the cumulative billiary and urinary excretions of acetaminophen, glucuronide conjugate [137].

Glycyrrhizin-Secretion of HBsAg and accumulated it dose-dependently in PLC/PRF/5 cells, chronic hepatitis B- suppressed the intracellular transport of HBsAg at the trans-Golgi area after O-linked glycosylation and before its sialylation, improved the liver histology, intracellular transport and suppresses hepatitis B virus surface antigen, prevents development of hepatocellular carcinoma in chronic hepatitis[138-139].
8β-glycyrrhetinic acid, an aglycone of glycyrrhizin decreases the expression of P450 E1 in CCl_4 induced liver injury thereby protecting the liver [140].
Glycyrrhizic acid in Concanavalin A -induced mouse model had effect on mice CD4(+)T cells in livers and spleens that showed inhibition of hepatic fibrosis[141].
Compound *glycyrrhizin* tablet improved the liver dysfunction that augmented the entire cytotoxic function mediated by hepatic lymphocytes inhibiting the cascade in HIV induced apoptosis. It inhibited cross-linking between HIV spikes and CD_4, a cell surface molecule, by suppressing CD_4 expression, and suppresses apoptosis [142]. *Glycyrrhizin* and *glycyrrhetinic acid* with interferon induction in mice showed activation of macrophages and augmentation of NK activity through the action of the induced IFN[143].
Prolonged use of excessive doses leads to pseudoaldosesteronism indicated with potassium depletion, sodium retention, oedema, hypertension and weight gain [144].

Luffa echinata* Roxb. (*Cucurbitaceae)

Various parts of Luffa are useful for the treatment jaundice, enlargement of liver and spleen, cirrhosis, dropsy. The active constituents are cucurbitacin, saponin, echinatin, β-Sitosterol, oleanolic acid and flavonoids.
Petroleum ether, acetone, methanolic and ether extracts of Luffa showed hepatoprotective activity in CCl_4 induced hepatotoxicity in albino rats [145-146]. Its crude extract has shown significant improvement in biochemical parameters in liver injuries [147]whereas the aqueous extract significantly lowered serum bilirubin levels in chlorpromazine induced jaundice in rats[148]. Its Hydro-alcoholic extract showed anti-hyperglycaemic activity along with improvement in renal and hepatic functions [149].

Moringa oleifera Lam (Moringaceae)

Drum stick plant is widely used as nutritional herb and contains rich source of the vitamin A, vitamin C and milk protein. Different types of active phytoconstituents like alkaloids, protein, quinine, saponins, flavonoids, tannin, steroids, glycosides, fixed oil and fats.
Extract showed protection against cadmium-induced toxicity in rats [150]. Aqueous extract restored the lead perturbations through reduction of oxidative stress–induced DNA damage via amelioration of NF-kB and TNF-α which kept hepatocyte integrity and reduced serum hepatic enzyme activities [151]. Ethanolic extract of leaves enhanced the recovery from hepatic damage induced by antitubercular drugs [152], prevented and improved liver damage[153]. Methanolic leaf extract showed antioxidant and dose-dependent hepatoprotective activities in CCl_4 model [154].

Nigella sativa* L. *(Ranunculaceae)

Bleck seed has been used as antihypertensive, liver tonics, diuretics, digestive, anti-diarrheal, appetite stimulant, analgesics, anti-bacterial. The active compounds are thymoquinone, thymohydroquinone, dithymoquinone, p-cymene, carvacrol, 4-terpineol, t-anethol, sesquiterpene longifolene α-pinene and thymol *etc*

Basal diet with *Nigella sativa* addition in lead nitrate induced toxicity showed protective effect against toxic effect of lead on liver and kidney tissues [155]. Aqueous extract showed hepatoprotective effects in nimesulide and paracetamol induced hepatotoxicity [156-157]. Volatile oil in CCL_4 induced hepatotoxicity decreased the lipid per-oxidation and liver enzymes, increased the anti-oxidant defence system activity [158].

Hydro-alcoholic extract 0.2 mL/kg by intraperitoneally administration in the rats protected the rat liver against to hepatic ischemia-reperfusion injury [159].

Hepato protective activities of water extract were observed in rats with CCl_4-challenged damage[160], with 5-(Aziridin-1-yl)-2,4-dinitrobenzamide (CB 1954) hepatotoxicity[161], and Balb/C mice transplanted with the 66cl-4-GFP cell line for antitumor activity[162].

Thymoquinone from NS showed hepato protective effect in acetaminophen induced hepatotoxicity [163-164]& supplementation prevents the development of DENA-induced initiation of hepatic carcinogenesis by decreasing oxidative stress and decreased mRNA expression of GSHPx, CAT and GST [165].

Thymoquinone orally as well as intraperitoneal, LD_{50} of both in mice and rats by the method of Miller and Tainter, was found relatively a safe compound, particularly when given orally[166-167]. Fixed oil of NS did not show any -LD_{50} - acute or chronic toxicity [168].

Phyllanthus niruri Linn& species (Euphorbiaceae)

Phyllanthus is probably the most widely explored genus for liver disorders. Recognized for its role in viral hepatitis, *P. niruri* is used in ASU systems for different biliary conditions and in preventing gallbladder calculi. It contains flavonoids, terpenoids, alkaloids, polyphenols, lignans, tannins, saponins, coumarins.

Hot water extracts showed antioxidant activity and the protective effect in paracetamol-induced liver damage [169] [240]. Aqueous leaves extract modulated the expression of matrix metalloproteinases in alcohol and thermally oxidized polyunsaturated fatty acid-induced hepatic fibrosis [170].

In CCl_4 induced liver damage fresh leaves juice, aqueous and methanolic extracts of seeds showed hepatoprotective effects[171-172] and ethanolic extract of aerial parts showed subsequent recovery towards normalization in Swiss strain female albino mice[173-174].

Hepatoprotective effects were also observed in ethanolic extract of whole plant except root in aflatoxin B_1-induced liver damage in mice [175] and in thioacetamide induced liver cirrhosis in rats [176]. Hepatoprotective effects of methanolic, aqueous extract of the leaves and phenolic constituents were observed in ethanol-induced oxidative damage in adult male wistar albino rats with glucuronidation in rats [177]. Extracts significantly inhibited hepatocarcinogenecity induced by N- nitrosodiethylamine in a dose dependent manner [131].

Hepatoprotective and mechanistic benefits of Corilagin C_1, Isocorilagin C_2, Brevifolin C_3, Quercetin C_4, Kaempferolrhamnoside C_5, Gallic acid C_6, Brevifolin carboxylic acid C_7-CCl_4 induced toxicity in Clone-9 and Hepg2 cell lines were observed [178].

Protein isolate had hepatoprotective effect in acetaminophen and CCL_4 -induced toxicity[179-180].

Phyllanthin showed antioxidant capability of rat hepatocytes including level of total glutathione, and activities of SOD and glutathione reductase ethanol-induced hepatotoxicity in rats [181].

Picrorhiza kurroa* Royleex Benth. (*Scrophulariaceae)

Rhizomes of ***Kutaki*** are bitter in taste, cooling and use for removal of excessive *Pitta* from the body via colon. It helps in restoration of Liver functions by overcoming fatty liver changes.

The bioactive compounds of plants are iridoids-icroside I, picroside II, picroside III, picroside IV, kutkoside, pikuroside, cucurbitacin and acetophenones.

Aqueous-ethanolic extracts protected hepatotoxicity induced by acetaminophen in Cockerels[182],aqueous extract in liver slice culture system; ethanol restored the activities of antioxidant enzymes and significantly reduced lipid peroxidation [183]. Its extract significantly inhibited hepatocarcinogenecity induced by N-nitrosodiethylamine in a dose dependent manner [131].

Hydroalcoholic extract in non-alcoholic fatty liver disease showed reversal of the fatty infiltration of the liver and lowering of the quantity of hepatic lipids [184].

Picoliv has shown significant hepatoprotective effects in alcohol and paracetamol induced hepatotoxicity in rats [185-187], aflatoxin B_1-induced liver damage in mice [188] and choleratic effect with increase in bile flow & change in the physical properties of the bile secretion [189]. ***Picroliv or Kutkin*** again showed hepato-protective and immune-modulator activities in D- *g*alactosamine, paracetamol, thioacetamide and CCl_4 induced hepatic damage [190].

In hepatic amoebiasis associated with CCl_4 toxicity it showed hepato-generative effect[191] and decreased the levels of lipid peroxides and hydroperoxides and facilitated the recovery of superoxide dismutase and glycogen [192-194].

The hepatoprotective and bile flow enhancing activity of Kutkin- iridoid glycoside have been demonstrated[195].

Piper longum L.(Piperaceae)

Long pepper (one of the three ingredients of *Trikatu*- pungent herbs), used as a *Rasayana,* is useful in respiratory & digestive disorders. The fruits contain volatile oil, resin and alkaloids piperine and piperlonguminine.

Traditional milk extract– dried fruits boiled with milk – showed protective effect in CCl_4 induced hepatotoxicity [196]. *Piperine*- major active constituent-bio enhancer activity- protects against hepatocellular injury and fibrosis [197-198].

Piperine showed showed regeneration process by restricting fibrosis in CCl_4 and tertiary butylhydroperoxide induced hepatotoxicity; but offered no protection against acute damage or against cirrhotic changes [199].

LD_{50} values of Piperine on adult male mice showed that most animals died of respiratory paralysis within 3–17 min, while in sub-acute toxicity studies, the rats died within 1–3 days after treatment. In histopathology severe haemorrhagic necrosis and oedema in gastrointestinal tract, urinary bladder and adrenal glands observed. Death may be attributable to multiple dysfunctions in organs [200].

Plumbago zeylanica* L.(*Plumbaginaceae)

Root of Plumbago, is considered a strong digestive stimulant that helps relieve indigestion, gas, bloating, cramping and constipation, a detoxifier - blood purifier being effective against liver flukes. Roots of the plant contain an acrid crystalline principle called plumbagin, chloroplumbagin and biplumbagin.

Hepatoprotective effects are observed of rhizome extracts in CCl_4-induced [201-202]] and Petroleum ether extract in paracetamol induced liver damage [203].

In acute and sub-acute-toxicity studies with petroleum ether, acetone, and the hydro alcoholic extracts no mortality was observed with acute safe dose but liver and kidney were adversely affected following the sub-acute administration of root extract in rats[204].

Swertia chirata Buch Ham(Gentianaceae)

It is a bitter tonic, carminative, laxative, anti-pyretic, febrifuge, anti-periodic, anti-inflammatory, stomachic, and anthelmintic used in treating various types of fevers, liver diseases, piles, skin diseases, ulcers, and

diabetes. The main chemical ingredients are Swertiamarin, Amarogentin, Swechirin, Mangiferin, Sweroside, Gentianine, Amaroswerin, Oleanolic acid, Swertanoone, Ursolic acid.
Ethanolic extracts improvised levels of serum marker enzymes in paracetamol-induced hepatotoxicity [205-206].
Syringaresinol- Methanolic extract showed anti-hepatotoxic activity against CCL4, galactosamine and paracetamol induced liver toxicity [207-208].

Tephrosia purpurea* (L.) Pers.(*Fabaceae)
It is cholagogue, deobstruent, diuretic, tonic and laxative; and used in enlargement and obstruction of liver. It contains rutin, purpurin, purpurenone, quercetin, retinoids, deguelin, elliptone, rotenone, sitosterol, and tephrosin. It protects the liver against drug induced oxidative damage probably by increasing antioxidative defense activities.
Variety of hepatoprotective effects of whole plant aqueous extract in paracetamol-induced[209], Ethanol extract of roots in CCl_4 induced[210], Hydro-alcoholic extract against sodium arsenate induced sub-acute toxicity[211] and Aqueous-ethanolic extract of aerial parts in thioacetamide induced liver cirrhosis in rats[212] have been observed.

Terminalia chebula* Retz (*Combretaceae)
Haritaki is principal ingredient of *Triphala* (combination of three fruits) that is recognized for a wide range of cathartic effects. It improves metabolism and provides beneficial effects to colon, liver, spleen and lungs.
T. chebula is of pyrogallol (hydrolysable) type; contain 14 components of hydrolysable tannins. Water extract prevented liver toxicity in anti-tuberculosis drug-induced toxicity (Sub-chronic administration of rifampicin, isoniazid and pyrazinamide in combination)[213] and in den induced hepatocellular carcinogenesis in experimental rats[214].
It prevents acute and severe liver injury, inhibition of oxidative stress and inflammatory cytokines with membrane stabilizing activities in C57/BL6 mice model of tert-butylhydroperoxide induced acute liver injury [215]. It exhibited chemo preventive potential by estimating the levels of lipid peroxidation and assaying activities of various marker enzymes in paracetamol-induced liver damage [216].
Ethanolic fruit extract showed hepatoprotective effect in ethanol-induced hepatotoxicity in rats [217] whereas *chebulic acid* showed antioxidant effect in isolated rat hepatocytes [218], tannins flavonoids expressed protective mechanism in N-nitrosodiethylamine induced-hepatocellular carcinoma [219].
Crude alcoholic extract did not exhibit any ***cytotoxic effect*** to fresh sheep erythrocytes cytotoxins in alliums model or any ***genotoxic effect*** in either vitotox test or Ames assay [220-221].

Tinospora cordifolia (Willd.) Miers (Menispermaceae)
Guduchi is probably known as one of the best-known immunomodulatory plant from Ayurveda. A variety of active components like alkaloids, steroids, diterpenoid lactones, aliphatics, and glycosides have been isolated from different parts of the plant.
Whole plant aqueous extract benefitted in bile duct ligation induced jaundice in rats [222]. Hepatoprotective effect of water extract was observed in CCL_4 induced liver toxicity in goat [223]. Aqueous extract showed protective effects in hepatic and gastrointestinal toxicity induced by chronic and moderate alcoholism [224]; significant improvement in Kupffer cell function using carbon clearance test showed a trend towards normalization [225]. Aqueous, petroleum ether and ethanol extracts of various parts of the plant prevented liver toxicity in CCL_4 damage [226-227]. Ethanolic extract showed hepatoprotective effect in CCl_4 induced liver damage in mice, rat, and rabbit [228-231]. Protective role of stem and leaves extract was observed in lead nitrate

induced toxicity[232], aflatoxin-induced nephrotoxicity on thiobarbituric acid reactive substances levels with increase the level of GSH, ascorbic acid, protein, the activities of anti-oxidant enzymes[233].

Zingiber officinale* Roscoe (*Zingiberaceae)

Ginger is a spice consumed worldwide for culinary and medicinal purposes contains Phenols, Oleoresins, Zingiberene, Zingiberole.

Hepatoprotective and antioxidant effects of ethanolic extract of Ginger rhizomes have been observed in CCl_4, acetaminophen, paracetamol and thioacetamide induced liver toxicities in rats[234-237].

Dry ginger with essential oils – phenols, flavonoids components studied in DEN - induced hepatocellular carcinogenesis in rats reduced the severity cytotoxicity and anticancer potential against HepG2 cell line [238].

The detoxicating action of Ginger in liver was found to be more effective therapeutically on cadmium toxicity, accumulated cadmium, than prophylactically [239]

Significance of pharmacological models and plants studied

Animal models have played an important role in biomedical research as crucial tool for study and understanding the pathogenesis of several liver diseases, help to develop new pharmacologic treatments. Each model in vivo and in vitro has several characteristics, advantages and limitations.

Table 1. summaries of several experimental models for hepatoprotective and hepatotoxicity activities and plants listed from above observations

No.	Model & Plants	Relevance	Possible activities	Limitations
1.	CCL_4[240] (21)	Metabolized by cytochrome P-450 in endoplasmic reticulum, mitochondria with the formation of ccl3o	Reactive oxidative free radical-initiates lipid peroxidation	Prolonged treatment promotes severe cirrhotic changes with significant development of Ascites
2.	Paracetamol [240] (18)	Analgesic- antipyretic lipid peroxidative degradation of glutathione level	Produces cell necrosis	Produces Acute liver damage in high dose
3.	Acetaminophen [241] *(6)*	Encountered drug hepatotoxicity	Reactive metabolite formation, Mitochondrial damage, DNA fragmentation, Necrosis	Overdose leads to liver failure, death
4.	Ethanol[242]*(5)*	Steatosis, elevation of CYP2E1, oxidative stress, increases gut permeability, activates LPS-TLR4-Kupffer cells	Mild elevation of serum ALT, AST, Low levels of liver inflammation	Lack of ability to develop ALD
5.	Alcohol[243]*(5)*	Changes in membrane lipid composition, fluidity, increase hepatic lipid peroxidation	Mild liver injury, steatosis, low-grade liver inflammation	Dehydration, low blood alcohol level, inadequate nutrition

6.	Thioacetamide[244] *(5)*	Interfere the movement of RNA from the nucleus to cytoplasm	Membrane injury, reduces the number of viable hepatocytes, rate of oxygen consumption, decreases the volume of bile	Long time to develop, Slow reversibility
7.	Anti-tuberculosis drug- Isoniazid and rifampicin[245] *(4)*	Oxidative stress, Produced steatosis, increased SDh, indicated mitochondrial injury	Adverse effects on the liver, ranging from mild transient elevations in aminotransferases to overt hepatitis	Pathogenesis underlying hepatotoxicity poorly understood
8.	Aflatoxin B_1/ Hepatotoxin[246] *(4)*	Toxin-dependent liver injury, hepatic GH-resistance	Dose-dependent wasting, stunting, liver pathology, suppression of hepatic targets of GH signalling	Epoxide from binds with protein may lead to Compensatory liver hyperplasia, promote the incorporation of mutations into the DNA
9.	Galactosamine[247] *(4)*	Diffuse type of liver injury simulating viral hepatitis, disrupts the synthesis of essential uridylate nucleotides	Reduces the number of viable hepatocytes, rate of oxygen consumption Tnfα-mediated apoptosis Inflammatory liver injury	Difficulties with reproducibility, refractory anaemia
10.	DEN, NDEA[248-249] *(4)*	Progression of liver fibrosis to HCC	Generation of ROS resulting in oxidative damage to macromolecules	Vary with the genetic background, sex, age, other factors
11.	tBHP[250] *(3)*	Oxidative Stress	Inhibition of complex I activity peroxidation of membrane lipids, deplete cellular GSH	More sensitive to the exogenous source of oxidative injury
12.	Malathion[251] *(2)*	Cytotoxicity, genotoxicity	Inhibition & accumulation of acetyl cholinesterase activity, leading to the interference with the transmission of nerve impulse	Toxic to other beneficial insect species, highly toxic to aquatic invertebrates
13.	Lead nitrate[252] *(2)*	Produce Oxidative damage by enhancing per oxidation of membrane lipids	GSH depletion, elevation in biochemical parameters	Acute intoxication with Pb^{2+} caused disturbance in the body metabolism
14.	Chronic alcohol[253] *(1)*	Easy to perform Marked elevation of ALT, steatosis	Liver injury, inflammation, fatty liver	Mild steatosis, slight elevation of serum ALT Short-term feeding with no mortality rate, No liver fibrosis

15.	Na ASO_2[254-255] *(1)*	Induction of apoptosis, inhibition of tumor cell growth	Activity of 20S proteasome, decreased protein expression of PSMB5, SOD1, GPXL	Carcinogenicity
16.	Cisplatin[256] *(1)*	Solid organ malignancies, Oxidative damage, Increase in the release of pro-inflammatory cytokines	Accelerate the apoptotic process, cellular damage	Yet not clear
17.	Bleomycin[257]*(1)*	Inhibit fibrosis - interrupting the cell cycle	Inflammatory, fibrotic reactions, induction of pro-inflammatory cytokines	Molecular alteration
18.	Chlorpromazine[240] *(1)*	Activation of Toll-like receptor signalling by LPS, LTA	Significant induction of serum TNF) α , prolonged JNK activation	Interference with metabolism
19.	Cadmium[258]*(1)*	Benign, malignant tumor formation	Increased activities of serum hepatic marker enzymes, level of lipid peroxidation indices	Genetic damage in cultured mammalian cells
20.	Nimesulide[259]*(1)*	Non-steroidal anti-inflammatory drug	Preferential inhibitory activity on COX-2 enzyme	Increased risk for hepatotoxicity
21.	Arsenic[260] *(1)*	Apoptosis	Hepatocellular injury, fatty degeneration, progressive fibrosis	Carcinogenicity
22.	High Fat diet (HFD)[261] *(1)*	Induction of liver injury	Higher plasma ALT, AST, hepatocyte hypertrophy, lipid droplet accumulation, necrosis, inflammatory cell infiltration	Associated with obesity, diabetes, insulin resistance, steatosis, steatohepatitis, cirrhosis

DISCUSSION

Liver disease is a worldwide problem. Conventional medicines used in the treatment of liver diseases are sometimes inadequate, may lack efficacy and can develop serious adverse effects. Prevention is a preferred strategy than cure. A series of review papers have been published by *authors* pertaining to liver disorders, therapeutics and medicinal plants used in the treatment of liver diseases with elaborate compilation of classical, proprietary and patented Ayurvedic products [2-7]. These reviews also summarised the information about hepatoprotective herbal drugs used in ASU traditional medicine for the treatment of liver diseases.

In this comprehensive review an effort has been made to provide all-inclusive information on liver disorders and potential medicinal plants used for liver diseases in all the three - *ASU* classical texts, pharmacopoeias and national formularies. Most potential twenty-five medicinal plants are assessed for its phytochemical and pharmacological activities in a comparative and summarised manner for its potentials to develop the safety and effective products [262].

Classical or poly herbal formulations

Due to synergism, the best combination of poly-herbal have various types of molecules provide higher activity against a disease to act against a disease complex as in liver dysfunctions by different mechanisms. Several of the large numbers of herbal and herbo-mineral formulations in different dosage forms used for different liver diseases in ASU Systems are studied for their hepatoprotective activities and safety. ASU classical formulations such as *AmalkyadiGhrita*[263], *Arogyavarghini*[264],*Emblica officinalis* and Chyavanaprash[265,266],*AruvadhaChurnam*[267], *Chara Parpam*[268], *KadukkaiMaathirai*[269], *Dawa-Ul-Kurkum*[270], *Habb-e-Asgand*[271],and *Sharbat-e- Deenar*[272]. No adverse effects have been reported with proper administration of designated therapeutic dosages.

Ayurvedic proprietary products like SAL [273], Liv 52[274], Ayush-Liv. 04[275], *Jigrine*[276], *Kabideen Syrup*[277]and *Patented BV-7310*[278]have been studied for their hepatoprotective activity against hepatotoxins like carbon tetrachloride, paracetamol, anti-tuberculosis drugs in rat, mice and rabbit models. More than 24 clinical papers and 92 experimental studies on Liv 52, 21 cases of hepatitis and 45 cases of surgery related hepato-biliary disorders treated with an Ayurvedic drug L 2002 (Livotrit) [279, 280] and an open study on 10 patients of alcoholic hepatitis with drug Hepafyte [281] suggest significant role of poly herbal formulations in liver dysfunctions.

Extracts

Though aqueous, alcoholic, methanol, hydro-alcoholic, petroleum ether and chloroform extracts are most commonly used for testing of 18, 15, 10, 5, 4 and 3 medicinal plants respectively and hydro-methanol, acetone and ether extracts in a plant each. Essentially aqueous extracts of most commonly used *A. paniculata, C. longa, N. sativa* are found to be effective for their different hepatoprotective activities. A traditional recipe of *P. longum* boiled with milk, the ethanol extract of ginger and Cinnamomum bark rich in oil are found to be hepatoprotective. Five different extracts of *A. vera, E. alba, L. echinta* and four different extracts of *G. glabra* have been studied.

Due to high polarity and miscibility with organic solvent water is the most polar solvent used in the extraction of a wide range of polar compounds. It dissolves a wide range of substances. It is cheap, nontoxic, non-flammable, and highly polar. *Alcohol* is also polar in nature, miscible with water, and could extract polar secondary metabolites. *Chloroform* is a nonpolar solvent and is useful in the extraction of compounds such as terpenoids, flavonoids, fats, and oils, while Ether is useful in the extraction of compounds such as alkaloids, terpenoids, coumarins, and fatty acids [282-283].

Phytoconstituents

Liver protective plants contain a variety of chemical constituents like phenols, coumarins, lignans, essential oil, monoterpenes, carotinoids, glycosides, flavonoids, organic acids, lipids, alkaloids and xanthenesetc.One or more phytoconstituents of ten plants have been studied in-vivo or in-vitro for hepatoprotective effects. *A. panniculata* tops the list of phytoconstituents with andrographolide (I), andrographiside (II) and neoandrographolide (III), andrographolide and derivatives followed Azadirachtin-A, Nimbolide, Nimbolide and nimbic – 4 from *AI*. Berberine hydrochloride, sanguinarine from *BA* and curcumin from *C.longa* are found to have a variety of hepatoprotective activities both in acute and chronic conditions. Coumestans (wedelolactone and dimethyl wedelolactone extracted from *E. alba* is found to have anti-cytotoxic activity and regenerative activities. Glycyrrhizin and glycyrrhetic acid probably are the most extensively studied phytoconstituents for a variety of and mostly complimentary hepatocytic activities useful in hepatic dysfunction. Picroliv from *kurroa* and phyllanthin from *Phylanthes*species are probably the most known

hepatoprotective plants investigated for viral hepatitis. *Kalunji*, a common dietetic article with medicinal properties has thymoquinone, a studied hepatoprotective. Syringaresinol from *chirayta* a well-known antipyretic plant is also studied for its hepatoprotective activity. Piperine from *P. longum* has added value as a bio-enhancer for its hepatoprotective activity.

Pharmacology models its significance

CCl_4 and APAP also termed paracetamol are the most commonly used experimental models for the evaluation with hepatoprotective and antioxidant activity. Lipid peroxidation is considered a critical factor in the pathogenesis of liver injuries [284]. CCL_4 model is widely used because of the inhibition of the radical CCl_3 enervation in the protection against the damage generated, while APAP model is the highly reproducible, dose-dependent hepatotoxicity of APAP and its outstanding translational importance, because acetaminophen overdose is one of the most frequent reasons for ALF in human. Several new animal models are now available to study specific types of liver damage.

Activities

Most of the hepatoprotective plants have antioxidant activity. *Amala* in addition to having NAFLD activity is protective against heavy metal toxicities like one due to Arsenic. The famous immune-modulator *T. cordifolia* is effective against hepatotoxins, particularly due to anti-tuberculosis drugs. *EA* interestingly is found effective in HCV infection and against hepatotoxins (aflatoxins). Curcuma, Cichori, *Kutaki* has distinct activity in NAFLD. Luffa having anti-hyperglycaemic activity could be of interest; strong anti-toxicity activity of Cinnamomum may justify its role as an additive in many formulations.

The activities of the plant drugs could generally be classified as -

1. Anti-hepatotoxic- antagonize the effects of any hepato toxins
2. Hepatotropic-promote the healing process of the liver
3. Hepatoprotective prophylactic-prevent liver affections

It is clearly established that medicinal plants and phytoconstituents can treat chronic liver disease by inhibiting oxidative damage, suppressing fibrogenesis, eliminating virus infection, and preventing or inhibiting tumors' growth. ASU formulations and ingredients not only prevent liver damage but also reverse the damage as evidenced by the scientific studies.

Toxicity

Aloe was surprising reported to be carcinogenic in a single study, use of Berberis, Neem, Cichorium require care with higher doses and long term use the other plants *C.longa, P.kurro, P. zeylanica, T. chebula* have been variably studied for safety. It has been observed that the extractives of several of these plants have been reported to be toxic as in case of *P. zeylanica* root where petroleum ether, acetone and hydro-alcoholic extracts showed Hepatic and renal changes[285].

CONCLUSIONS

The present review can be concluded as follow-

1. Liver diseases in ASU systems have an interesting philosophical background with a long history. The significance of the liver in the context of blood as an important factor for liver dysfunction.
2. Natural origin ingredients have been extensively used in ASU traditional medicine for the treatment of liver diseases. Due to synergism, the best combination of poly-herbal provides higher activity by different mechanisms to provide a complete therapy against liver diseases.

3. Medicinal plants contain a complex blend of phytochemicals that have the unique ability to address a multiplicity of problems simultaneously. The activities of plants are most likely due to their internal complexity and to the interactions of the different components within the body rather than to one of its specific components.
4. Comparatively broad-spectrum benefits and safety as observed in many studies on polyherbal and aqueous extracts as used in traditional medicine do raise questions about use of solvent extracts. Extracts may concentrate one or two isolated constituents which having particular activity but inadvertently overlook some other components that may contribute the same as activity of the whole drug. The issue of standardization could be addressed with advances in analytical methods.
5. Need to develop new pre-clinical models to justify integrative approaches to examine specific liver dysfunction is felt to enhance research in liver disorders.
6. Ayurveda, Siddha and Unani systems offer highly promising translational opportunities to develop and validate new therapeutics for treatment for liver diseases. The need is to stimulate new research by bridging fundamentals of traditional systems with the advances in biotechnology to explore richness of natural products and ingredients.
7. This review will helpto consider new methods for safe and cost-effective formulations not only as hepatoprotective remedies but to better treat serious liver diseases as well.

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