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A review on hepatoprotective and Anti-HIV action of traditional herbs to reduce the hepatotoxicity of highly active anti-retroviral therapy (HAART)

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Abstract
Drugs are well thought-out to be one among the significant causes of liver injury and drug-induced hepatotoxicity may result in asymptomatic elevation of liver enzymes to hepatic failure. In the present scenario, the advent of highly active antiretroviral therapy (HAART) has dramatically reduced morbidity and mortality among patients with advanced human immunodeficiency virus infection. However to date, hepatotoxicity has been associated with all currently used antiretroviral (ARV) drug regimens. Therefore it is the need of this hour to seek for solutions from ancient herbs that has been reported to have anti-retroviral as well as hepatoprotective activity in order to maximize the benefit and minimize the risk of highly active antiretroviral therapy (HAART). Since age-old times, medicinal plants play a significant role against on various diseases. The traditional Siddha system of medicine is one among the oldest traditional system which holds enormous literary evidences of various medicinal herbs that have potent hepatoprotective activity. The present article explores the scientific basis for the traditional literature evidences on the hepatoprotective and antiretroviral action of selective herbs so that they can complement in reducing the hepatotoxicity of conventional antiretrovirals.

Keywords: Herbs, HIV, hepatoprotective, highly active antiretroviral therapy, siddha, antiretroviral therapy

1. Introduction
Drugs accounts for 20-40% of all instances of fulminant hepatic failure resulting in liver transplantation and death. Presently more than 900 drugs, toxins, and herbs have been reported to cause liver injury. The drug-induced hepatotoxicity may result in highly variable manifestations such as asymptomatic elevation of liver enzymes to hepatic failure [1]. The advent of highly active antiretroviral therapy (HAART) has dramatically reduced the clinical impact of infection with HIV and there has been declining morbidity and mortality among patients with advanced human immunodeficiency virus infection [2]. However, to date, hepatotoxicity has been associated with all currently used antiretroviral (ARV) drug regimens. The prescribing information for all Protease inhibitors (PIs) approved by the US Food and Drug Administration (FDA) includes the warnings such as hepatitis, hepatic failure and death, increased risk for alanine aminotransferase and/or aspartate aminotransferase (ALT/AST) elevations in patients with pre-existing liver disease or underlying hepatitis B virus (HBV) or hepatitis C virus (HCV) infection [3]. In spite of remarkable pace in modern medicine, there are hardly any drugs that stimulate liver function, offer protection to the liver from damage or help regeneration of hepatic cell. In this scenario, Ethno pharmacology can be sought as an imperative element for developing nation`s medical and economic system. Since ancient times, medicinal plants play a significant role against on various diseases. The Siddha system of medicine is one among the oldest traditional system which holds enormous literary evidences of various medicinal herbs that have potent hepatoprotective activity. Presently the World governments are being encouraged to seek a synthesis between modern and traditional medicine. Hence the present review has been made with a focus on complementing medicinal herbs with hepatoprotective action to target against drug induced hepatotoxicity. Here, a list of hepatoprotective plants with their reported active chemical components and their possible underlying mechanism are tabulated in table1.

1.1 Highly active antiretroviral therapy (HAART) and Hepatotoxicity
Till date, an arsenal of 24 Food and Drug Administration (FDA)-approved drugs are available for treatment of HIV-1 infections. Based on their molecular mechanism and resistance profiles, these drugs are distributed into six distinct classes:

(1) nucleoside-analogue reverse transcriptase inhibitors (NNRTIs), (2) non–nucleoside reverse transcriptase inhibitors (NNRTIs), (3) integrase inhibitors, (4) protease inhibitors (PIs), (5) fusion inhibitors, and (6) coreceptor antagonists [4]. **S**uppression of the HIV replication by highly active antiretroviral therapy (HAART) in patients co-infected with HCV/HBV causes elevation of transaminase levels causing complex immune changes that alter the response against hepatitis virus antigens. The contribution of each particular drug to the development of hepatotoxicity in a HAART regimen is difficult to determineand **t**he incidence of liver toxicity is not well known for most of the antiretrovirals [5]. One study found hepatitis to occur with a similar frequency among Zidovudine/Lamivudine, Zidovudine/Didanosine, or Stavudine/Lamivudine patients [6] whereas a separate study found a higher incidence of hepatotoxicity among Stavudine/Lamivudine patients [7]. Hepatic events were the most common drug ADRs associated with Atazanavir/Ritonavir. Jaundice was also observed among Atazanavir/Ritonavir patients [8].

2. Materials and Methods

The manuscript was prepared after an extensive survey of literature using traditional Siddha literature ad search engines such as Pubmed, Google scholar, Embase, Scopus, Elsevier AND science direct and the obtained results were critically analyzed and discussed.

3. Discussion

3.1 *Phyllanthus niruri*

Phyllanthus niruri is a time-honoured herbaceous plant of Euphorbiaceae family that belongs to the various regions of India and Sri Lanka. Since ancient times, the herb, *P. niruri* has been and is used widely for the treatment of Jaundice. A research study by Tona *et al.* claimed the antimalarial activity of *P. niruri in vivo* [8]. The study performed by Odetola and Akojenu reported the Anti-diarrhoeal and gastrointestinal potentials of the aqueous extract of *Phyllanthus amarus* (Euphorbiaceae) [9]. The Hepatoprotective action of the intraperitoneal administration of aqueous extract of *Phyllanthus niruri* against nimesulide-induced hepatic disorder in mice was determined by estimation of glutamate oxaloacetate transaminase (GOT), glutamate pyruvate transaminase (GPT) and alkaline phosphatase (ALP) in serum and also by measuring the hepatic content of the antioxidant enzymes, superoxide dismitase (SOD) and catalase (CAT), reduced glutathione (GSH) and thiobarbituric acid reacting substances (TBARS). The study results suggested that mice administered with P. niruri significantly restored the altered levels of those anti-oxidant molecules suggestive of hepatoprotection against nimesulide induced oxidative stress. Moreover, one of the latest study suggested that the *Phyllanthus niruri* extract treated mice showed less necrotic central vein and reduced inflammations in the livers when compared with nimesulide treated mice that showed larger and balloon like hepatocytes [11-14]. Combining all, the data suggest that *P. Niruri* possesses protective role against nimesulide induced hepatic damage in mice [10]. Likewise, *Phyllanthus niruri* extract also showed protection against paracetamol-induced hepatotoxicity in fishes pretreated with *Phyllanthus niruri* when compared to control and the Protein isolate of *Phyllanthus niruri* indicates hepatoprotective effect against acetaminophen-induced toxicity [15].

Naik AD reported that the alkaloidal extract of *Phyllanthus niruri* inhibited the growth of both HIV-1 and HIV-2 strains cultured on human MT-4 cells [16]. Also, the water alcoholic extract of *Phyllanthus amarus* was found to be a potent inhibitor of HIV-1 replication in HeLaCD4+ and also inhibited the RT inhibitor-resistant HIV strains. The inhibitory effect of *Phyllanthus amarus* against HIV strain was both *in vitro* and *in vivo* [17-19] Niruriside, a novel compound isolated from *Phyllanthus niruri* was initiate to exert inhibitory effect against the binding of REV protein to RRE RNA with an IC50 value of 3.3 μM and thus exerts anti-HIV action [20].

3.2 *Andrographis paniculata*

Andrographis paniculata belongs to the family Acanthaceae is a bitter herb. The whole plant part has a wide application in the Siddha system of Indian medicine as a hepatoprotective and hepatostimulative agent. It is also used in some other countries like Java, Malaysia, Indonesia and elsewhere in the United States. The plant is chiefly found in plains throughout India from Himachal Pradesh to Assam and Mizoram, West Bengal, and all over South India [21]. The plant has been reported to exhibit various mode of biological activities *in vivo* as well as *in vitro viz*., antibacterial, antiviral, anti-inflammatory, anti HIV (Human immunodeficiency virus), immunomodulating/immunostimulatory and anticancer. The plant showed potential therapeutic action in curing liver disorders, common cough and colds in human [22]. In 1993, Shukla *et al.* found that andrographolide has a significant dose-dependent protective activity against paracetamol-induced toxicity on *ex vivo* preparation of isolated rat hepatocytes [23]. In the same year Kapil *et al.* proved the protective effects of *A. paniculata* on hepatotoxicity induced in mice by carbon tetrachloride [24]. Several research studies reveal that the aqueous extract of *A. paniculata* inhibited BHC induced liver toxicity in Swiss male mice (Trivedi *et al*., 2007; Trivedi and Rawal, 2000; Sutha *et al*., 2010) and ethanol induced hepatotoxicity in albino wistar rats. Andrographolide offered protection against galactosamine or paracetamol induced toxicity to hepatic tissue [25-27]. A conducted Phase I dose-escalating clinical study of Andrographolide from *Andrographis paniculata* conducted in 13 HIV positive patients (not taken antiretroviral medications during the trial) and five HIV uninfected, healthy volunteers with the objectives to assess safety and tolerability and secondarily to assess effects on plasma virion HIV-1 RNA levels and CD4(+) lymphocyte levels. At the end of the study, the reports showed a significant rise in the mean CD4 (+) lymphocyte level of HIV subjects occurred after administration of 10 mg/kg Andrographolide indicating that the phytoconstituent Andrographolide may inhibit HIV-induced cell cycle dysregulation, leading to a rise in CD4(+) lymphocyte levels [28]. Researchers conducted by Stephen and Comac indicated that extracts of Andrographis paniculata may have the potential for interfering with the viability of the Human Immuno Deficiency Virus (HIV) and advised that *A. paniculata* could combine with modern medicines against Acquired Immuno Deficiency Syndrome (AIDS) [29].

3.3 *Phyllanthus emblica*

Phyllanthus emblica L. (PE) is a tree that belongs to the family Euphorbiaceae and is distributed throughout the tropical and subtropical regions of Deccan, coastal districts, Kashmir and deciduous forests of Madhya Pradesh in India [30]. The plant has been reported to contain phytochemicals such as quercetin, gallic acid, corilagin and ellagic acid are also reported to protect against the cytotoxic effects of

paracetamol, microcystins, galactosamine and lipopolysaccharide. Several scientific studies have shown Phyllanthus emblica to impart beneficial effects on liver function and to ameliorate the toxic effects of hepatotoxic agents like ethanol, paracetamol, carbon tetrachloride, heavy metals, antitubercular drugs etc. It has been reported to possess protective effects against chemical-induced hepatocarcinogenesis in experimental animals [31]. The hepatoprotective effect of PE extract was evaluated by Leo *et al*., using Ethanol -induced hepatotoxicity model, since it induces clinically relevant effects in the liver leading to Alchoholic liver diseases. Chronic administration of ethanol led to a significant elevation of serum levels of ALT, AST, and ALP. The rise in the ALT level is usually accompanied by the conversion of amino acids to keto acids and decrease in the levels of total protein (TP) indicating the destruction in the number of hepatic cells, which may result in a decrease in hepatic capacity to synthesize protein. Alcohol intoxication-mediated oxidative stress causes peroxidation of cell membrane lipids and alters phospholipid membrane permeability which allows the leakage of various enzymes including ALT, AST, and ALT into blood circulation. The above study confirmed that PEE possesses effective antioxidant activity against free radicals that can be attributed to the presence of gallic acid, ellagic acid, polyphenols, and flavonoids and therefore provides significant protection against alcohol-induced liver damage which is further supported by histopathological observations. The *E. officinalis* extract was found to be hepatoprotective, due to its membrane stabilising, antioxidant and CYP 2E1 inhibitory properties. Treatment of rats with *E. officinalis* extract (75 mg kg-1 per day) also enhanced liver cell recovery by bringing the levels of AST, ALT and IL-1β back to normal.

Inhibition of HIV-Reverse Transcriptase (HIV-RT) by *E. officinalis* plant extract fractions was tested on Peripheral Blood Mononuclear Cells. With this test it was observed that aqueous fraction and n-hexane fraction have highest inhibition of recombinant HIV-RT (91% and 89%, respectively) at 1 mg/ml concentration. Chloroform fraction showed highest inhibition of HIV-RT at 0.5 mg/ml and carbon tetrachloride fraction at 0.12 mg/ml concentration. At 0.12 mg/ml and 0.5 concentrations 50% of the HIV-RT activity is inhibited in n-hexane fraction and carbon tetrachloride fraction respectively [32]. Our results demonstrate that compared to the standard anti-HIV drug AZT, a *P. emblica* shows highest inhibition of HIV-RT at 0.5mg/ml and CTF fraction at 0.12mg/ml concentration. These data are consistent with the results of one previous study on the inhibition of HIV infection by medicinal plant extracts [33].

3.4 *Azadirachta indica*

Azadirachta indica is rapidly growing evergreen plant found commonly in India, Africa and America [34]. Neem is native of India andnaturalized in most of tropical and subtropical countries are of great medicinal value and distributed widespread in the world. The non-wood products such as leaves, bark, flowers, fruits, seed, gum, oil are known to have anti-allergenic, anti-bacterial, anti-viral, anti-fungal, anti-inflammatory, anti-diabetic, mosquito-repellent activity, larvicidal, spermicidal and other biological activities. Earlier finding confirmed that Neem and its constituents play role in the free radical scavenging and in the prevention of several diseases [35]. The chemical constituents contain many biologically active compounds that can be extracted from neem, including alkaloids, flavonoids, triterpenoids, phenolic compounds, carotenoids, steroids and ketones, biologically most active compound is Azadirachtin, it is actually a mixture of seven isomeric compounds labelled as Azadirachtin A-G and Azadirachtin E is more effective [36]. The ingredients of Neem also play a pivotal role as hepatoprotective without any adverse effects. A study was performed to investigate the hepatoprotective role of Aazadirachtin-A in carbon tetrachloride (CCl4) induced hepatotoxicity in rats and histology and ultra structure results confirmed that pre treatment with Azadirachtin-A dose-dependently reduced hepatocellular necrosis. Furthermore results of the study show that pretreatment with Azadirachtin-A at the higher dose levels moderately restores the rat liver to normal [37]. In HIV/AIDS patients, oral administration of acetone water Neem leaf extract for a period of 12-weeks had a significant influence *in vivo* on CD4 cells without any adverse effects in the patients. The mean levels of CD4 cells increased by 159% in 50 patients, which is a significant improvement. The number of HIV/AIDS pathologies decreased from the 120 baseline to 5 and significant increases were experienced in body weight (12%), haemoglobin concentration (24%), and lymphocyte differential count (24%) [38]. The crude extract of Neem exhibited strong HIV-1Reversed transcriptase inhibitory activity. At concentration of 50 and 100µg/ml the extract significantly reduced 0.005% polymerase activity of the recombinant HIV-1 RT with the peak inhibition of 92.4% at 100µg/ml. Neem oil is also used as a nonspecific immunostimulant as it plays a role in the activation of cell-mediated immune mechanisms to obtain an enhanced response to subsequent mitogens.

3.5 *Cedrus deodara*

Cedrus deodara (family Pinaceae) is one of the globally significant and most widely planted genera. The plant is mainly used for production of essential oils, for various medicinal and pharmaceutical purposes [39]. The essential oil of Cedrus is antiseptic, calming and a diuretic. The essential oil helps in urinary tract infections, hair loss, cellulite, tuberculosis, dandruff, catarrh, arteriosclerosis, dentifrices, psoriasis, and fungal infections and as anti-inflammatory, analgesic, immunomodulatory and sedative agents [40]. The phytoconstituents of cedar wood oil show spasmolytic, hepatoprotective, antioxidative properties. Volatile oil of *Cedrus deodara* at a dose 50 and 100mg/kg drastically slow down neutrophil adhesion to nylon fibers and also inhibit arthus reaction of type III hypersensitivity reaction i.e., induced by methylated bovine serum albumin and it also inhibit the sheep erythrocytes and oxazolone induced delayed type hypersensitive reaction [41]. Anti-inflammatory activity of the essential oil of the wood of *C. deodara* was studied on rats. The results from the study indicated that essential oil extracted from the wood of the plant exhibited significant anti-inflammatory action against carrageenan-induced inflammation at a dose of 50 mg/kg and 100 mg/kg, respectively [42].

3.6 *Alpinia galanga*

Alpinia galanga (Linn.) of Zingiberaceae family is one amongst those medicinally important plants. *Alpinia galanga* commonly found in Indonesia, India, China, and Arabic gulf areas, Malaysia, Egypt and Sri Lanka [43]. It grows in open, sunny places, forests and brushwood. *Alpinia* demands much attention from the researchers towards the development of potential therapeutics against various diseases like cancer, diabetes, ulcer and many neural disorders. The genus possess

ample of flavonoids, tannin and other polyphenolics which extend its biological effectiveness towards anti-inflammatory, antimicrobial, anticancerous and other therapeutic potentials [44]. Several active compounds such as 1'S-1'-acetoxychavicol acetate, 1'S-1'-acetoxyeuginol acetate, 1, 8-cineol, α-fenchyl acetate, β-farnesene, β-bisabolene, α-bergamotene, β-pinene, β-Sitosteroldiglucoside (AG-7), β-sitsterylArabinoside (AG-8), 1'-acetoxychavicol acetate (galangal acetate), p-hydroxycinnamaldehyde has been extracted from the plant [45]. It was found in most of the reports and reviews that were surveyed Galangin is an active pharmacological ingredient from propolis and Alpinia officinarum. Hence, and has been reported to have anti-inflammatory and antioxidative properties. The present study aims to reveal the effect of galangin on Concanavalin A (ConA)-induced hepatitis (CIH), a well-established animal model of immune-mediated liver injury, and to clarify the related mechanism. C57BL/6 mice were pretreated with galangin followed by ConA challenge. Results indicated that galangin inhibited ConA-induced liver damage. Mice pretreated with galangin showed more reduction of liver damage when compared with control mice pretreated with vehicle solution. In galangin-pretreated mice with induced CIH, increases in serum levels of several inflammatory cytokines, including tumor necrosis factor-α, interferon-γ, and interleukin-12 were dramatically attenuated, and chemokines and adhesion molecules like interferon inducible protein-10, macrophage inflammatory protein-1α, and inter-cellular adhesion molecule-1 messenger RNA expressions in liver were decreased. Moreover, CIH mice pretreated with galangin showed less leukocyte infiltration and T-cell activation in the liver. Moreover in another study, it has been observed that the hepatoprotective effect of the crude extract of Alpinia galanga at 200 and 400 mg kg-1 treated paracetamol induced hepatotoxicity in rats [46]. A Study by YE, 2006, shows that 1'S-1'-acetoxychavicol acetate (ACA), a small molecular compound isolated from the rhizomes of Alpinia galanga, inhibited Rev transport at a low concentration by binding to chromosomal region maintenance 1 and accumulating full-length HIV-1 RNA in the nucleus, resulting in a block in HIV-1 replication in peripheral blood mononuclear cells. Additionally, ACA and didanosine acted synergistically to inhibit HIV-1 replication. Thus, Alpinia galangal may correspond to a novel treatment for HIV-1 infection, especially in combination with other anti-HIV drugs [47].

3.7 *Momordica charantia*

Momordica charantia Linn. Is a monoecious climber found in tropical and subtropical regions, often under cultivation up to an altitude of 1500m. It is mainly found in Africa, Asia and Australia. Its fruits, seeds and leaves are traditionally used to treat diabetes mellitus across India [48]. The efficacies and molecular mechanisms of bitter gourd-induced anti-diabetic, anti-HIV, and antitumor activities were reported to be contributed by over twenty active components were determined. The Anti-HIV properties of the fruit pulp extract of *Momordica* was studied *in vitro* and was found as a potent inhibitor of HIV-1 replication [49]. The hepatoprotective role of Momordica extract in our findings seems to be due to enhanced antioxidant enzymes as reported by Semiz and Sen [50]. In another study by Dandagi and co-workers explored the hepatoprotective activity of various extracts of *Ferula asafetida, M. charantia* and *Jatamansi* against experimental hepatotoxicity and the results demonstrated that the extracts of *Momordica charantia* Linn. Had noteworthy hepatoprotective activity [51]. Similar results were also observed by Thenmozhi and Subramanian as they studied the antioxidant and hepatoprotective potential of *Momordica charantia* fruit extract in ammonium chloride-induced toxicity in rats [52]. Studies by Hossain *et al*., 2011 confirmed that the hepatoprotective activity of *Momordica charantia* may be attributed due to the presence of flavonoids, ascorbic acid and other components such as saponins, tannins, triterpenes and alkaloids [53]. The above findings of researches were also in supported by Chaudhri *et al*., who reported that the serum level of these liver enzymes (ALT, AST, ALP) is elevated in CCl4 intoxicated rats however hydro- alcoholic extract of M. charantia again reduced amounts of theses enzymes to normal level indicating its hepatoprotective effect [54]. It is, therefore, suggested that *M. charantia* may be used as an inexpensive remedy for the liver diseases in developing countries but further studies should be carried out to assess its pharmacological aspects. Besides the hepatoprotection offered by *Momordica charantia*, it has also been shown to inhibit HIV-1 reverse transcriptase due to its protein coded as MRK29 [55].

3.8. *Glycyrrhiza glabra*

Glycyrrhiza glabra is native to Eurasia, northern Africa and western Asia [56]. The Leaves of *Glycyrrhiza glabra* were used externally for the treatment of wounds. Rhizome and root were used orally to treat cystitis, kidney stones, lung ailment, diabetes, cough, stomachache, gastric ulcers, tuberculosis, Addison's disease; it was also used as mild laxative, contraceptive and to improve sexual function [57]. In addition, it was also used in sore throat, influenza, cold, bronchodilator, opthalmia, anti-syphilitic, antidysenteric, gastric imbalance, indigestion, vomiting, diarrhoea, swollen abscesses and as diuretic [58]. The preliminary qualitative phytochemical screening of the ethanolic extract of *Glycyrrhiza glabra* root revealed the presence of alkaloids, glycosides, carbohydrates, starches, phenolic compounds, flavonoids, proteins, pectin, mucilage, saponins, lipids, tannins, sterols and steroids [59]. The hepatoprotective potential of aqueous (QGG) and ethanol extract of *Glycyrrhiza glabra* (EGG) and their possible mechanism were studied in rats hepatotoxicity. For acute hepatopathy, rats were intraperitoneally injected with CCl4 at a dose of 1.0 ml/kg as a 50% olive oil solution. The rats were orally given the aqueous and ethanol extract of *Glycyrrhiza glabra* at doses of 250, 500 mg/kg after 6 h of CCl4 treatment. At 24 h after CCl4 injection, samples of blood and liver were collected and then biochemical parameters and histological studies were carried out. The results revealed that both extracts inhibited significantly the activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) which elevated by CCl4 and increased the activity of superoxide dismutase which decreased by CCl4 [60]. The hepatoprotective effect of aqueous extract (2gm/kg/day orally for 7 days) of *Glycyrrhiza glabra* roots was investigated in rabbit models with acute liver injury induced by carbon tetrachloride at a dose of 1.25 ml/kg. Aqueous extract of Glycyrrhiza glabra had a significant effect in amiolerating liver functions as well as restoring hepatic tissue in acute liver diseases [61]. The hepatoprotective and antioxidant potential of Glycyrrhiza glabra hydro-methanolic root extract were investigated against carbon tetra chloride induced oxidative-stress mediated hepatotoxicity in liver tissue of Swiss albino mice. The results suggested that, the crude extract of root of *Glycyrrhiza glabra* at the doses of 300 and 600mg/kg bw for 7 days possessed significant hepatoprotective potential against

CCl4 induced oxidative stress mediated hepatotoxicity [62]. In another study, *Glycyrrhiza glabra* extracts and glycyrrhizic acid inhibited the replication of several viruses included Epstein-Barr virus, Herpes simplex virus, Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, Human cytomegalovirus, Human immunodeficiency virus, Influenza virus, SARS coronavirus and Varicella zoster virus [63]. In a study by Hatano 1988, two coumarins of *Glycyrrhiza glabra*, glycocoumarin and licopyranocoumarin, inhibited giant cell formation in HIV-infected cell cultures without any cytotoxicity. Lichochalcone A also had anti-HIV activity [64]. Glycyrrhizin was investigated as a therapy of human immuno-deficiency virus (HIV) in 42 hemophilia patients with HIV-1 infection. Patients showed improvement in their clinical symptoms (oral candidiasis, lymph node swelling and rash), immunological functions and liver functions.

4. Conclusion

While modern medicine offers a wide number of benefits still it is often limited in as it carries the risk of adverse effects, and is often too costly for the developing world. Hence the management of HAART induced hepatotoxicity can be reduced to a greater extent by synergistically combining conventional antiretrovirals with traditional herbs that have hepatoprotective as well as antiretroviral action. In this review article, an attempt has been made to compile the reported hepatoprotective plants which may be useful to develop evidence-based alternative medicine to reduce the drug induced hepatotoxicity especially in patients with Acquired immune deficiency syndrome (AIDS).

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