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HERBAL OPTIONS FOR THE MANAGEMENT OF DRUG INDUCED LIVER DAMAGE. A REVIEW

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Summary

Liver damage due to ingestion or inhalation of hepatotoxin such as drugs is increasing worldwide, and conventional drugs used in the management of drug induced liver damage are mostly inadequate and have serious adverse effects. In spite of the tremendous strides in modern medicine, there are grossly few drugs that stimulate liver function, offer protection to the liver from damage or help regeneration of hepatic cells. It is necessary to search for herbal drugs which could be used for the management of liver damage to replace or complement currently used drugs of low efficacy and safety. According to the World Health Organization estimations, around 80% of the world's population depends on herbal medicine for their primary health care largely due to its cheapness and wide availability. This present review was undertaken to search for the major herbs used around the world with hepatoprotective effects which may be pursued for their clinical usefulness in the management of drug induced liver damage and other liver disorders. The search used keywords such as herbal medicine, hepatoprotective effects, each crossed with the term drug induced liver damage, with particular emphasis on experimental models, effective dosage and hepatoprotective effects of these herbal preparations. The search result revealed twenty-one of the major herbs with hepatoprotective properties which are *Flacoourtia indica, Annona squamosa, Silybum marianum, Cichorium intybus, Chamomile capitula, Coccinia grandis, Wedelia calendulacea, Prostechea michuacana, Cassia roxburghii, Orthosiphon staminens, Ficus caria, Lepidium sativum, Sargassum polycystum, Capparis spinosa, Allium sativum, Balanites aegyptiaca, Khala senegalensis, Prosopis Africana, Vitellaria paradoxa, Bauhinia racemosa and Chamomile capitula* (Table 2). Further research is necessary to elucidate the pharmacological principle of these herbs which will stimulate future pharmaceutical development of therapeutically beneficial hepatoprotective herbal drugs. Hepatoprotective herbs could be used as dietary adjuncts to existing therapy which will act as protective mechanisms against the development of drug induced liver damage.

Keywords: Hepatoprotective herbs, Drug induced liver damage, Management.

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Introduction

Chronic hepatic diseases is one of the foremost health problems worldwide, with liver cirrhosis and drug induced liver injury accounting for the ninth leading cause of death amongst the western and developing countries populations (1). About 20,000 deaths are reported every year due to liver disorders (2). Conventional drugs used in the management of drug induced liver damage are mostly inadequate and have serious adverse effects. It is, therefore, necessary to explore the herbal options in the management of drug induced liver damage to replace currently used drugs of low efficacy and safety.

Epidemiology and Statistics of Drug induced Liver Injury.

Drug induced liver damage is a health problem worldwide and is expected to increase as the number of drugs being consumed increases. It is a major health issue that challenges not only health care professionals but also the pharmaceutical industry and drug regulatory agencies (3). Drug induced liver injury is the most commonly cited reason for withdrawal of already approved drugs from the market (4). According to the United States Acute Liver Failure Study Group, drug-induced liver injury accounts for more than 50% of acute liver failure, with hepatotoxicity caused by overdose of paracetamol accounting for 39% and idiosyncratic liver injury triggered by other drugs accounting for about 13% (5). Drug-induced liver toxicity accounts for approximately half of the cases of acute liver failure and mimics all forms of acute and chronic liver disease (6). The reported incidence of anti-tuberculosis drugs induced hepatotoxicity indicated that the developing countries are having difficulties in systematic steps for prevention and management of tuberculosis drugs induced hepatotoxicity. Despite the frequency of drug induced liver injury being relatively low, data from the centers for disease control and prevention in the U.S reported approximately 1600 new acute cases of liver failure annually, of which Paracetamol hepatotoxicity accounts for approximately 41% (7).

Herbal Medicine and Hepatoprotection.

Herbal Medicine is a branch of science in which plant based formulations are used to alleviate diseases (8). Several authors have reported favourable results with hepatoprotective herbs (Table 2) either in animal or in human studies. Treating drug induced liver damage with plant-derived compounds which are accessible and do not require laborious pharmaceutical synthesis is highly attractive (1). Hepatoprotectives are a class of therapeutic agents that includes many synthetic and natural products used to protect against hepatic damage induced by various toxins. Natural resources such as plants are always considered and used in the search for new molecules to be used as drugs. Numerous medicinal plants and their formulations are used for liver disorders in ethnomedical practice as well as traditional system of medicine in India (9). Plant-based therapeutic agents like silybin, silymarin from *Silybum marianum* (milk thistle) are accepted and used worldwide as hepatoprotective (10). Silymarin is a flavonolignan that

has been introduced recently as a hepatoprotective agent. Silymarin is extracted from the seeds and fruits of *Silybum marianum* which is a mixture of three structural components: Silibinin, Silydianine and Silychristine (9). In India, about 40 polyherbal commercial formulations reputed to have hepatoprotective action are being used. It has been reported that 160 phytoconstituents from 101 plants have hepatoprotective activity (11). Liver protective herbal drugs contain a variety of chemical constituents like phenols, coumarins, lignans, essential oil, monoterpenes, carotinoids, glycosides, flavanoids, organic acids, lipids, alkaloids and xanthines (11). Plant extracts of many crude drugs are also used for the treatment of liver disorders. Extracts of different plants of about 25 plants have been reported to cure liver disorders (12). In spite of tremendous strides 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 (13). There are however, many drugs employed in traditional system of medicine for liver diseases (14). In the absence of reliable liver protective drugs in allopathic medical practices, herbs will play a good role in the management of various liver disorders most of which speed up the natural healing processes of the liver. Scientific evaluation of medicinal plants is important to the discovery of novel drugs and also helps to assess toxicity risks associated with the use of either herbal preparations or conventional drugs of plant origin. There is a growing interest in herbal remedies because of their effectiveness, minimal side effects in clinical experience and relatively low cost. Therefore, studies with plant extracts are useful to know their efficacy and mechanism of action and safety. Natural remedies from medicinal plants are considered to be effective and safe alternative management of drug induced hepatotoxicity.

The most commonly implicated drugs involved in acute liver injury are summarised in Table 1.

1. Paracetamol

Paracetamol overdose is the leading cause of drug-induced fulminant hepatitis among the United States **populations (15)**. Traditionally, it is believed that a minimum of 7.5 - 10g of paracetamol is needed to produce hepatic necrosis in an adult.

2. Augmentin (Amoxicillin/ Clavulanic acid)

According to various registries and retrospective studies in Augmentin is the most frequently reported antibiotic associated with drug induced liver injuries (DILI). The estimated risk of symptomatic hepatitis due to augmentin is less than 1 in 100,000 persons exposed. Age is found to be the most important determinant in the biochemical expression of augmentin-induced hepatotoxicity (16). Patients younger than 55 years of age exhibit predominantly hepatocellular damage, which occurs at 1 week after exposure to the drug while cholestatic liver injury occurs mostly at 2-3 weeks and the mixed liver injury proportionally predominates after 3 weeks.

Table 1: Commonly – reported drugs associated with drug induced liver injuries.

Paracetamol
Non-Steroidal Anti-Inflammatory Drugs Diclofenac Ibuprofen Naproxen
Antibiotics Amoxicillin/Clavulanate (Augmentin) Flucloxacillin Erythromycin Ciprofloxacin Anti-Tuberculosis Drugs (Isoniazid, Rifampicin, Pyrazinamide, Anti-Retroviral Drugs (E.g Ritonavir)
Immunosuppressant Azathioprine Cyclophosphamide
Anti-Arrthymia Drugs Amiodarone
Anti-Epileptics Phenytoin Carbamazepine Valproic Acid
Psychiatric Drugs Chlorpromazine Paroxetine

Source: (15).

3. Anti-tuberculosis drugs

Approximately 10 to 20 % of patients receiving isoniazid will develop mild to moderate elevation of ALT and about 0.1% develops clinical hepatitis **(15)**. The concomitant intake of rifampicin or pyrazinamide significantly increases the risk of liver disease from 2 to 4 %, which can be partly explained by an induction of CYP 450 enzymes. There is a continuous interest in hepatitis B as a risk factor for anti-tuberculosis drugs-related hepatotoxicity **(15)**. (17) reported that 2 to 4 % of patients treated with isoniazid, rifampicin and ethambutol developed symptomatic hepatitis of which, more than 35 % were hepatitis B carriers and about half of them developed liver failure subsequently. In contrast, the mortality rate for non-hepatitis B carriers was less than 4 %. Recent studies have shown that about 35 to 59 % of hepatitis B carriers will develop abnormal liver function tests during anti-tuberculosis treatment and 25 to 50 % of them are symptomatic **(15)**.

4. Thiazolidinediones

Thiazolidinediones are insulin-sensitising agents used to treat diabetes mellitus through activation of the gamma isoform of the peroxisome proliferators activated receptor (15). Troglitazone, the first approved Thiazolidinediones, was withdrawn from the market in 2000 following 94 reported cases of liver failure (15). An idiosyncratic mechanism of toxicity was suggested based on the delayed onset of ALT elevation and a lack of dose effect. Rosiglitazone and pioglitazone were introduced into the market by the time troglitazone was withdrawn and both did not show an increased risk of ALT elevation in early clinical trials.

5. Statin

Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are commonly used for hyperlipidaemia and form an important part of a preventative strategy against cardiovascular morbidity and mortality **(15)**. Asymptomatic mild ALT elevation is a class effect of statins, and it does not indicate liver dysfunction. Clinically significant hepatotoxicity caused by statins remains extremely rare. Hepatocellular, cholestatic and mixed patterns of liver injury have been documented. Although not evidence-based, current recommendations discourage the use of statins in patients with pre-existing liver disease. But this practice is problematic, because hyperlipidaemic patients have a significant prevalence of underlying NASH resulting in an elevated ALT level **(15)**.

Objectives of the Review Study

According to the World Health Organization estimations, around 80 % of the world's population depends on an alternative system of medicine for their primary health care. To rationalize the use of herbs in management of liver disorders, a scientific research on them is urgently needed. Therapies developed along the principles of western medicine are often limited in efficacy, carry the risk of adverse effects and are often too costly especially for the developing world (1). Scientific evaluation of medicinal plants are important to the discovery of novel drugs and also helps to assess toxicity risks associated with the use of conventional drugs. In spite of the tremendous strides 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 (13). Considering the economic resource constraints and cheapness of herbal products, this present review study was designed to review some herbal remedies used around the world for the management drug induced liver damage. Bearing in mind, that many modern pharmaceuticals used in conventional medicine today for the management of liver damage have natural plant origin. A review of hepatoprotective herbs from Nigeria and abroad will be useful to, the pharmaceutical industry, health care professionals and biomedical researchers in the field of pharmacology and therapeutics to develop herbal medicine to manage different kinds of drug induced liver disorders in man and animals.

Research Design and Methods

A comprehensive literature search was made from internet and serial materials of Nnamdi Azikiwe library, University of Nigeria, Nsukka. Different scientific Journal articles, proceedings of learned societies of ethnopharmacology and alternative therapy, World Health Organization documents and textbooks were consulted vis-à-vis of herbal medicine and management of drug induced liver damage. The search used keywords such as alternative therapies, hepatoprotective herbs and individual herb names from popular sources each crossed with the term drug induced liver damage. Experts in different fields were contacted to identify studies and hand searched references of key articles. Studies were limited to those articles published in the English language and restricted to search on herbs with hepatoprotective effects. The findings were presented in table 2.

Results

The search revealed twenty – one major species of herbs used around the world with hepatoprotective effects as gleaned from the scientific literature that is available. Table 2: shows the major herbs used around the world with hepatoprotective effects.

Discussion

Herbal based therapies for hepatoprotection has been in use for a long time and has been popularized world over by leading pharmaceuticals. Despite the significant popularity of several herbal medicine in general and hepatoprotective herbs in particular, they are still unacceptable treatment modalities for liver disorders. The limiting factors that contribute to this eventually are (i) lack of standardization of herbal drugs (ii) lack of identification of active ingredient(s)/principle (s) (iii) lack of toxicological evaluation. These results from lack of scientific based pharmacological data, most of the herbal formulations cannot be recommended for management of drug induced liver damage. There is no doubt that hepatoprotective medicinal herbs might provide an important source of new oral hepatoprotective compounds for development as pharmaceutical entities or as simple dietary adjuncts to existing therapies . There is need for more experimental and clinical studies on these identified hepatoprotective herbs from this search to enable isolation of their active principle, its mode of action, toxicity, drug interactions and side effects. Research on hepatoprotective herbs the world over is currently insufficient and requires more support from government agencies before the full potentials of this type of treatment can be realized in the management of drug induced liver damage the world over.

Table 2: Some hepatoprotective herbs that could be used for the management of drug induced liver damage.

Herb's Scientific Name(s)	Effective dosage	Animal model	Effect (s)	Reference (s)
1. *Flacoourtia indica*	1.5g/kg bw	Paracetamol induced rat	**Hepatoprotective**	**18**
2. *Annona squamosa*	300 & 350mg/kg bw	Isoniazid and rifampicin- induced hepatotoxic rats.	**Hepatoprotective**	**3**
3. *Silybum marianum*	Polyphenolic extract 25mg/kg	Thiocetamide-induced hepatotoxicity in rats	**Hepatoprotective**	**19**
4. *Cichorium intybus*	Polyphenolic extract 25mg/	Thiocetamide-induced hepatotoxicity in rats	**Hepatoprotective**	**19**
5. *Chamomile capitula*	Ethanolic extract 400mg/kg p.o.	Paracetamol induced liver damage in rats	**Hepatoprotective**	**2**
6. *Coccinia grandis*	Alcoholic extracts at 250mg/kg	Ccl_4-induced hepatotoxicity	**Hepatoprotective**	**20**
7. *Wedelia calendulacea*	Ethanolic extracts	CCl_4-induced acute hepatotoxicity in rats	**Hepatoprotective**	**21**
8. *Prostechea michuacana*	Methanol, hexane, & chloroform extracts 200, 400 and 600mg/kg	Ccl4-induced hepatic injury in albino rats. Paracetamol induced hepatotoxicity in rats.	**Hepatoprotective**	**22**
9. *Cassia roxburghii*	Methanolic extract 250mg/kg & 500mg/kg	CCl_4 induced hepatotoxicity in rats	**Hepatoprotective**	**23**
10.Orthosiphon staminens	Methanol extract 200mg/kg b.w	Paracetamol induced hepatotoxicity in rats	**Hepatoprotective**	**24**
11. Ficus caria	Methanolic extracts 500mg/kg b.w	ccl4 – induced liver damaged rats	**Hepatoprotective**	**25**
12. Lepidium sativuim	Methanolic extract 200 & 400mg/kg	Ccl4- induced liver damage in rats.	**Hepatoprotective**	**26**
13.Sargassum polycystum	Ethanol extract 125mg/kg b.w/day	D- galactosamine induced hepatitis in rats	**Hepatoprotective** .	**27**

14. Capparis spinosa	100, 200 & 400mg/kg	Ccl4 induced hepatic damage in mice	**Hepatoprotective**	**28**
15. Allium sativum	200g garlic/kg diet	Experimental lead exposed wistar rats	**Hepatoprotective**	**29**
16. Balanites acgyptiaca	100mg/kg b.w	Acetaminophen induced hepatotoxicity in wistar albino rats	**Hepatoprotective**	**30**
17. Khala senegalensis	100mg/kg b.w	Acetaminophen induced hepatotoxicity in wistar albino rats	**Hepatoprotective**	**30**
18. Prosopis africana	100mg/kg b.w	Acetaminophen induced hepatotoxicity in wistar albino rats	**Hepatoprotective**	**30**
19. Vitellaria paradoxa	100mg/kg b.w	Acetaminophen induced hepatotoxicity in wistar albino rats	**Hepatoprotective**	**30**
20. Bauhinia racemosa	Dose of 50, 100 & 200mg/kg	Paracetamol and ccl4 induced liver damage in rats.	**Hepatoprotective**	**31**
21. Chamomile capitula	400mg/kg p.o	Paracetamol intoxicated albino rats	**Hepatoprotective**	**2**

Conclusions

Therapies developed along the principle of western medicine are often limited in efficacy, the incidence of side effects are profound and often too costly, especially for the developing world populations. Physicians and patients are in need of effective therapeutic agents with low incidence of side effects which several hepatoprotective herbs potentially hold solutions to. Therefore treating drug induced liver damage with plant derived compounds which are accessible and do not require laborious pharmaceutical synthesis is highly attractive and should be a good direction to go for future researches. In this review article, an attempt has been made to compile some of the reported hepatoprotective herbs from around the globe and it will be very useful to health care professionals, scientists working the field of pharmacology and therapeutics to develop herbal medicine to cure different kinds of drug induced liver damage in man and animals. As we further our understanding of herbs, we might begin to develop a framework for a medical system capable of incorporating those herbal medicines proven to be beneficial in alleviating the suffering inflicted on humans by different diseases.

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