



Hepatoprotective Potential of *Hura crepitans* L.: A Review of Ethnomedical, Phytochemical and Pharmacological Studies

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Authors' contributions

This work was carried out in collaboration among all authors. Authors OSO and CL conducted all literature search. Author OSO drafted the manuscript. Authors CKF, CL, GK and BOM supervised and reviewed the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Herbal medicines are the main source of treatment of diseases in non-urban centres of the developing world. Secondary metabolites obtained from herbal sources contain bioactive phytochemicals, many of which have been the origin for the development of novel pharmaceutical drugs. *Hura crepitans* L. (Euphorbiaceae) or sandbox tree has been beneficial in many ethnomedicinal applications as a purgative, emetic, hepatoprotective, anti-inflammatory, antimicrobial and the treatment of leprosy. Toxicological, phytochemical and bactericidal studies

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have also been documented. This paper reviews the potential of the *Hura crepitans* plant in protecting the liver against drug-induced toxicity. The paper dwells extensively on the ethnomedical, phytochemical and pharmacological properties of the plant. In achieving the above, intensive analyses of books and published peer-reviewed journal articles were carried out using credible scientific databases. Four main phytochemicals were revealed to be contained in *Hura crepitans* stem-bark. Their protective effects were enunciated using animal models. However much more biochemical studies need to be done to establish the hepatoprotective potentials of the various parts and various phytochemicals of *Hura crepitans* with the need for more preclinical and clinical studies. We, therefore, present in this paper efforts to elucidate and bring to the fore the therapeutic potentials of *Hura crepitans* plant.

Keywords: *Hura crepitans* L.; toxicological assessment; phytochemical properties; hepato-protection.

1. INTRODUCTION

The liver is an organ involved in diverse functions that are important to life. Its significant roles include synthetic, secretory, metabolic and detoxification functions [1]. A compromise of any of these functions could engender liver diseases which have become a global public health problem [2]. Liver disease is a dysfunction of the liver and several types exist. They include hepatitis caused by viral infections and results in inflammations. Hepatitis A, Hepatitis B and Hepatitis C are viral Hepatitis types. Autoimmune hepatitis [3], which are primary biliary cholangitis and primary sclerosing cholangitis also exist. Liver cancers known as hepatocellular carcinoma [4,5] may present as bile duct cancer. Liver cell adenoma, another liver disease, is a tumour or a benign growth. There is also the occurrence of genetic liver disease which include hemochromatosis (too much iron in the liver), hyperoxaluria (too much oxalate in urine), Wilson's disease (copper accumulation in the liver and other organs) and alpha-1-antitrypsin deficiency. Other causes of liver disease include alcohol [6,7], drug overdose [8] and non-alcoholic fatty liver disease (NAFLD) evident by the accumulation of fat in the liver leading to inflammation.

Damage to the liver is generally characterized by necrosis of hepatocytes and increase in levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin and albumin which are all liver biomarkers [9]. Despite different kinds of liver diseases known, the progression of the disease irrespective of the aetiology is the same. Liver disease can be self-healing, but if that fails, then the usual progression is from healthy liver to inflammation, fibrosis, cirrhosis and end-stage liver disease (ESLD) which may lead to chronic liver failure. On rare occasions, liver failure can

occur suddenly (between 1-7 days). This is called an acute liver failure or fulminant hepatic failure, which could be as a result of ingestion of poison or drug overdose.

Chronic liver diseases are on the increase globally, leading to close to a million deaths per year [10]. More worrisome is that liver diseases contribute 24% of disease burden in sub-Saharan Africa [11].

There are several treatments for liver diseases. These include vaccines such as glycyrrhizin which inhibits hepatocellular carcinoma (HCC) progression and also interferon α -2b meant strictly for treatment of viral infections. Orthodox drugs available include cholagogues, choleretics, drugs for cholesterolic lithiasis, N-acetylcysteine and flavonolignans from *Silybum marianum*. Unfortunately, orthodox medicines have some challenges in the treatment and prevention of hepatopathies attributable to growing ineffectiveness; the growing cost of prescribed drugs [12,13]; toxicity and numerous side effects. Moreover, conventional drugs have failed to achieve desirable alleviating effects [14].

2. SOURCES OF INFORMATION AND CRITERIA FOR THE REVIEW

This investigation was carried out, between July 2016 and July 2019, by analyzing commonly consulted scientific books and published materials on ethnomedical, pharmacological and chemical characterization of *Hura crepitans*. Peer-reviewed articles were gathered by consulting the databases of SCOPUS, MEDLINE, Web of Science, PubMed, SCIENCE DIRECT and Google Scholar. The keywords employed to search for the literature of the databases included plant extract, hepatoprotective agents, *Hura crepitans*, inflammatory diseases and biomarkers. There were no

limitations regarding the language of publication in this search, however, most of the related studies were published in the English language. The criteria followed for the selection of reports in this paper include *Hura crepitans*: (i) in traditional medicine practice; (ii) its phytochemicals; (iii) with experimental anti-hepatotoxic effect; (iv) with LD₅₀ values reported in mass/mass; and (v) with LC₅₀ values reported in mass/volume.

3. PLANTS WITH HEPATOPROTECTIVE ACTIVITY AND THEIR MECHANISM OF ACTION

In Africa, medicinal plants are used for the management of liver ailments [15,16]. Nonetheless, except for a minor fraction, these hepatoprotective plants and mixtures used in traditional health practice are yet to be pharmacologically appraised in terms of their pharmacology, toxicity and effectiveness [17].

Those which displayed protection against the CCl₄-model in rats or mice include *Byrsocarpus coccineus* (Connaraceae) leaf decoction which is used for the management of jaundice in African herbal medicine [18]; aqueous extract of *Artemisia absinthium* L. has been demonstrated to have hepatoprotective activity against liver injury induced immunologically in mice [19]; aqueous extract of root tubers of *Daucos carota* L. was demonstrated by Bishaye, et al. [20] to have hepatoprotective effect on CCl₄-induced acute liver injury; methanolic extract of *Helminthostachys zeylanica* L. (Hook rhizomes) has been demonstrated by Suja et al. [21] to have protective effect against CCl₄-induced rat liver damage; aqueous root extracts of *Rhoicissus tridentata* L. was found to decrease the significant CCl₄-induced rise in aspartate transaminase and alanine aminotransferase while it increased significantly reduced glucose-6-phosphate [22]; protective influence of the ethanolic extracts of *Ziziphus mauritiana* Lam. leaves on CCl₄ liver damage in rats, through the lowering of the total bilirubin, lipid peroxide, aspartate aminotransaminase, alanine aminotransaminase and alkaline phosphatase levels [23]. Also, aqueous leaves extract of *Annona muricata* Linn. has been demonstrated to protect liver against CCl₄ and acetaminophen-induced damage in rats as well as protecting against hepatic jaundice [24]. Further, extracts of *Ficus pumila* Linn. [25] and *Ageratum conyzoides* Linn. [26] have been evaluated.

In humans, consumption of *Adansonia digitata* (baobab) fruit pulp has been found to exhibit substantial hepatoprotective activity through a mechanism adduced to triterpenoids, β-sitosterol, β-amyrin palmitate and ursolic acid found in its fruit pulp [27].

In paracetamol and thioacetamide models of hepatotoxicity, extracts of the seed of *Apium graveolens* L. have been shown to have hepatoprotective effect in rats, attributed to its ability to stabilize biological membranes [28]; leaf extract of *Cassia occidentalis* has been shown to possess significant hepatoprotective effect in paracetamol and ethyl alcohol-induced rat liver damage [29]; Olaleye, et al. [30] showed the hepatoprotective effect of *Alchornea cordifolia* (Schum and Thonn) leaf extract against acetaminophen-induced toxicity *in vivo* and adduced the hepatoprotective effect to the antioxidant properties of the herb.

Silymarin is a phytochemical which derives its name from its plant source, *Silybum marianum* (milk thistle). Silymarin, a cocktail of flavonoid complexes, can protect hepatocytes and cells of the kidney from the toxicity of xenobiotics [31]. Silymarin contains four isomers of flavonolignans: Silibinin, isosilibinin, silychristin and silydianin. The 60% silibinin content of silymarin confers on it its hepatoprotective properties [32] and has gained global acceptability as a hepatoprotective agent. Silymarin, in addition to its free radical scavenging properties, enhances antioxidative enzymes, which include superoxide dismutase and catalase, whilst it also inhibits lipid peroxidation [33]. Silymarin offers protection against various chemically and alcohol-induced hepatotoxicities [34]. Animal studies have shown the protective effect that silymarin confers on liver cells exposed to a wide range of chemical substances, especially tert-butyl hydroperoxide, acetaminophen (paracetamol), phenylhydrazine and carbon tetrachloride [35,36]. The proven hepatoprotective effect of silymarin makes it a gold standard for the evaluation of hepatoprotective effects of various phyto-chemicals.

4. *Hura crepitans*

The plant *Hura crepitans* (Sandbox tree) is an angiosperm belonging to the family of Euphorbiaceae (spurge family). Though it is a native of tropical America, it is now widely dispersed in tropical rain forests. It is fondly

planted in the cities and villages for its shade. Apart from the name sandbox tree, it has several other names all over the world. Some of them include possumwood, "monkey's dinner bell" and "monkey's pistol". In Nigeria, it is known as "aroyin" by the Ijesa people. It is known as "abro koyin" by the Akan-Fante people of Ghana, and popularly called "okafo odidi" by most Ghanaian folks. The tree has sharp spiny stem bark which makes it also to be called "monkey no-climb".

Hura crepitans can grow to heights 35 to 60 meters depending on the environment. The leaves of mature Ghana cultivar can be as large as 9 inches and a foot long. The leaves are monoecious and are characterized by red flowers without petals. It has pumpkin-shaped fruits which are about 2 inches long and 3 inches in diameter and made up of 10 to 16 carpels. The carpels house seeds that are hard and flattened. The seeds of the fruit are dispersed by explosive mechanism when dried. *Hura crepitans* tree, fruit and seeds are shown in Fig. 1.

5. COMMON MEDICINAL USES OF *Hura crepitans*

Hura crepitans has been used in traditional therapy as purgative, antimicrobial, emetic, in the treatment of leprosy, as anti-inflammatory and hepatoprotective agents [37].

Studies on the toxicity, bactericidal properties and phytochemical screening have been reported [38,39]. The two lectins contained in the plant juice have haema-glutinating activity capable of inhibiting synthesis of proteins. The plant contains huratoxin, used for catching fish in different parts of the world. From the sap of *Hura crepitans* have been extracted hexahydrohuratoxin and keto-enal. Hurain, a proteolytic enzyme and crepitin a toxic toxalbumin have also been isolated from *Hura crepitans* sap [40,41]. In a study conducted in 2009, it was found that the sap of *Hura crepitans* has been used by the Amazons of Peru in the treatment of mucousy diarrhoea in both dogs and humans. The sap has also found use as a worm expeller in both dogs and humans but found to be an effective remedy for stomach aches only in dogs [42].

6. CHEMISTRY OF *Hura crepitans*

Man is surrounded in nature by plants that are a natural chest of medicines. Though several drugs have been derived or designed from herbal

medicines, there still abound several yet to be fully investigated or even exploited plants for medicinal purposes. One of such plants is the sandbox tree (*Hura crepitans*). It is our considered opinion that spirited efforts be made by all and sundry to unravel through regulated and concerted research efforts, the great healing potentials locked up in this herb. This is being advocated because there is a paucity of data on the phytochemistry and the pharmacological properties of this herb.

Phytochemicals found in the leaves and stem bark of methanolic crude extracts of *Hura crepitans* were phenolics, alkaloids and steroids. Flavonoids, cardiac glycosides and tannins were found to be present in the stem bark but absent in leaves. Saponins and carbohydrates were however reported to be beyond detectable limit [43]. Leaf essential oil obtained through hydrodistillation was colourless and analysed by GC and GCMS analyses to contain 7 compounds with ethyl propionate being in the largest percentage and followed by isopentyl alcohol as shown in Table 1.

Up to date, few researchers may have made significant contributions to the knowledge of the pharmacological effects of *Hura crepitans*. Growing interests in seeking alternative therapies from herbs, drew the attention of Oloyede and Olatinwo [44] to investigate the antioxidant potentials of *Hura crepitans*. Employing sequential fractionation methods using solvents of ascending polarities, crude methanolic extracts were partitioned into various fractions with distilled water, hexane, ethyl acetate and butanol. The researchers went on to demonstrate that the crude methanolic extract and other fractions possessed antioxidant properties, using radical scavenging effect on 2,2- diphenyl-1-picrylhydrazyl (DPPH) and hydroxyl radical generated by hydrogen peroxide. The researcher concluded that *Hura crepitans* extracts' antioxidant property was mainly due to its ability to act as a hydroxyl scavenger, while it had weak activity as a donor of hydrogen, compared to the standards used. Specifically, it was suggested that *Hura crepitans* extract and fractions have antioxidant potentials which inhibit the oxidative damage caused by hydroxyl radical in most biological systems; the ethyl acetate and butanol fractions being the most effective in this respect. In another study using brine shrimp lethality test, it was shown that LC₅₀ values less than 1000 ug/ml were non-toxic while values greater than 1000 ug/ml was found to be toxic. The *Hura*

crepitans stem-bark hexane fraction was shown to be the most toxic while the ethyl acetate fraction of its leaves was shown to be the least toxic. It was later concluded from that study that *Hura crepitans* extracts could be used in the treatment of tumours [42]. In the same study, the investigators demonstrated that the stem-bark and the leaf of the herb had bactericidal and anti-fungal properties, with the stem-bark extract being the more potent [42].

Uchiyama and colleagues [45] obtained the bioactive compound in *Hura crepitans* stem-bark; 6,7-epoxy-5-hydroxyresiniferonol-14-(2,4-tetradecadienoate) also called daphne factor F3 (Fig. 2). They showed that *Hura crepitans* extract and the constituent active compound, daphne factor F3, inhibits neurotrophin-4 (NT-4) activity, thus improving hair regrowth in mice implanted with dihydrotestosterone (DHT). Their study showed unequivocally that *Hura crepitans* or its active compound has ameliorative effect on

androgenetic alopecia (AGA) [45]. The mechanism by which *Hura crepitans* exerts the effect of hair growth has not been fully elucidated especially as it concerns NT-4 expression in the hair follicles of mice in which there have been implantation of DHT [45]. The mechanisms and activity of androgen receptor (AR) and NT-4 that is inhibited by *Hura crepitans* has also not been sufficiently demonstrated. Moreover, the diterpene esters of daphne usually cause irritations of the skin and could act as tumour promoter [46]. Quite recently, Oloyede and others in their quest to drive home the point of the various ethnomedicinal potential benefits of the *Hura crepitans* plant, isolated some chemical constituents of its stem-bark and went on to show that *Hura crepitans* could protect against liver induced damages [37]. Daphnane, diterpenes; daphnetoxin acid, huratoxin apocynin and methylpentadecanoate were documented as isolated phytochemicals in their study [37].



Fig. 1. *Hura crepitans*: Tree, seeds and fruits

Table 1. Chemical constituents of the volatile oil from the leaves of *Hura crepitans**

Peak number	Compound	RRI	% composition
1.	Ethyl butyrate	0172	4.3
2.	Ethyl propionate	0126	39.6
3.	Isopentyl acetate	0238	0.5
4.	Isopentyl alcohol	0134	10.6
5.	Isopentyl butyrate	0204	2.4
6.	Methyl butyrate	0130	0.5
7.	n-Octene	0166	8.2
Total			66.1%

*Percentages calculated from the flame ionization detection data. RRI, relative retention indices calculated against n-alkanes. Oloyede and Olatinwo [43]

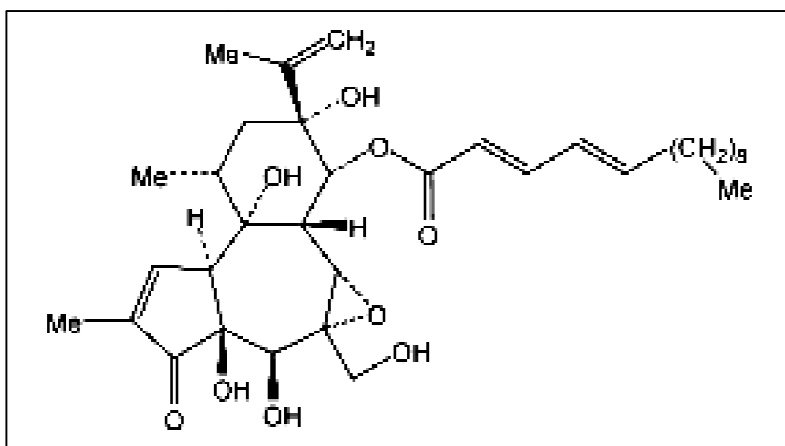


Fig. 2. Chemical structure of Daphne Factor F3

Source: Uchiyama et al. [45]

It is the opinion however that much more profound biochemical research still need to be done to establish the hepatoprotective potentials of the various phytochemicals of *Hura crepitans*. This tree planted traditionally in the tropical rain forests essentially for the shade which its canopy offers may yet turn out to be a great discovery in the quest for alternative healing remedies.

7. TOXICITY OF *Hura crepitans*

The toxicity of this plant is caused by two toxic albumins (toxalbumins), hurina and crepitina, which are distributed among all the plant organs [40,47]. The latex or sap from the tree has the diterpene hura-toxin which is toxic. Phytohaemagglutinin of *Hura crepitans* has crepitin which has been isolated. Contained in the seed of *Hura crepitans* is a glucosamine, lectin which has mitogenic and haemagglutinating properties [40,41].

8. HEPATOPROTECTIVE POTENTIALS OF *Hura crepitans*

The use of phytochemicals for therapeutic purposes dates back to ancient times. *Hura crepitans*, despite its well documented ethnomedicinal properties, has not been the focus of researchers, which has caused a dearth of data on the healing property of this plant. Though the antioxidant properties had been reported [44], the hepatoprotective effect of this plant was not considered for a long time. Because of its proven antioxidant properties, *Hura crepitans* would no doubt protect cells against reactive oxygen species which culminate

in free radical generated oxidative stress and provoke cell damage [48]. Antioxidants from nature exert a remarkable effect on proper health care and the avoidance of both chronic and degenerative diseases, amongst which are atherosclerosis, cardiac and cerebral ischemia, rheumatic disorders, carcinogenesis, neurodegenerative disorders, diabetes, DNA damage and ageing [49,50]. Plant-derived polyphenolic compounds from dietary sources are more efficient antioxidants *in vitro* than vitamin E or C and consequently may contribute immensely to defensive effects against organ damage *in vivo* [51,52]. Quite recently, however, the group whose previous investigations had suggested the anti-tumour properties of *Hura crepitans* [42], turned the searchlight in the direction of the anti-hepatotoxic properties of the plant using animal models [37]. They showed that *Hura crepitans* effectively influenced some biochemical parameters that contribute to hepatocellular damage and deduced that the plant had hepatoprotective properties. They also showed that the soluble ethylacetate fractions of the stem- bark of *Hura crepitans* had the greater hepatoprotective effect than for the leaf extracts. *Hura crepitans* has also been shown to have anti-inflammatory effect on rat paws [52].

9. USES OF *Hura crepitans* SEED

The *Hura crepitans* seed has been reported to cause burning sensations to the throat and also induce vomiting [53]. However, when properly treated, it is a good protein source for animal feeds [53]. Adedire and Ajayi [54] have also shown the food potential and physicochemical

properties of *Hura crepitans* seed. The seed oil has also been demonstrated to be useful for industrial purposes [55]. Proximate mineral and fatty acid compositions in addition to antimicrobial properties of *Hura crepitans* seeds have also been determined using standard methods [56].

Igwenyi et al. [57], examined both the antidiabetic and the hepatoprotective properties of ethanolic extract of *Hura crepitans* seed (HSE), in alloxan-induced diabetic rats. They found HSE to possess both antihyperglycemic and hepatoprotective effects in a dose-dependent manner. Although the mechanism by which HSE was able to produce these effects were not elucidated, they speculated that HSE contained antioxidants which were able to modulate enzymes responsible for glucose metabolism and also upregulate secretion of insulin by the pancreas. They were able to demonstrate that derangements in serum liver enzymes were mitigated in a dose-dependent manner after administration of HSE for 2 weeks. They also suggested that the hepatoprotective effect of HSE was due to its antioxidant effect and its free radical scavenging potential.

10. CONCLUSION

In spite of all the progress made by pharmaceutical industries in the development of novel and highly potent drugs in the treatment of a wide range of diseases, the patronage of herbal medicines has been on the increase all over the globe. With increasing interests in herbal therapy coupled with so many promising drug candidates of natural origin, it would be worth the while to intensify researches that would lead to the unearthing of novel and highly potent drugs to counteract diseases. The paucity of data on the therapeutic effect of *Hura crepitans* should further stimulate interests in the *Hura crepitans* plant. This review would no doubt be valuable in charting a course in future research endeavours on the therapeutic potentials of *Hura crepitans*. The body of evidence has demonstrated that *Hura crepitans* plant possesses the potentials to attenuate derangements brought about by diseased state associated with liver dysfunction.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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