RJMP Research Journal of Medicinal Plants

OPEN ACCESS

Medicinal Plants and Their Finished Marketed Herbal Products Used for Treatment of Liver Diseases in Ghana; A Field Survey and Review

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ABSTRACT

Background and Objective: Hepatic disorders are conditions that affect the structure or function of the human liver. Causes include microbes and their toxins, ionizing radiations and abuse of drugs. Medicinal plant products have been an alternative for the management of these diseases due to the expensive, unavailability and harmful side effects of pharmaceutical drugs. The aim of this study was to determine whether plant species used in preparing herbal medicinal products for treatment of liver diseases have reported hepatoprotective activity. **Materials and Methods:** A field survey was conducted using information from television, radio and market vans to identify the medicines and purchase them from the herbal shops. The plant species and parts used in manufacturing were extracted from the product insert and the Traditional and Alternative Medicine Council logbook. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) instrument was adopted in conducting the review. A search was conducted on Google Scholar, PubMed and Elsevier databases on hepatoprotection activity of the plant species. **Results:** In all, 175 articles met the criteria for the quantitative synthesis and were used for the review. For the plants, 56 species were used by 20 manufacturing companies in producing 25 herbal medicinal products. *Khaya senegalensis* was the most predominant plant species (9/25, 36.0% products). In terms of parts, leaves (40/56,71.4% of plant species) were the most prevalent part used. On databases, 41/56 (73.2%) plant species had hepatoprotective activity while 15 (26.8%) had no data for hepatoprotective activity. *Crataegus oxyacantha* was the plant species with the most parts reported parts (7 different parts). *Moringa oleifera* was most extracted (7 different solvents) and most tested against hepatotoxicity induced with 20 different toxicants. **Conclusion:** There is sufficient scientific data on the hepatotoxicity activity of plant species used for herbal formulations against liver disorders. Practitioners and Researchers should focus on isolation and testing of the active phytochemicals.

KEYWORDS

Hepatic, Herbal, toxicant, solvent, medicinal, hepatotoxicity

ISSN: 2151-7924 (Online)
ISSN: 1819-3455 (Print)
https://doi.org/10.3923/rjmp.2024.13.23

Received: 19 Feb. 2024
Accepted: 19 May, 2024
Published: 20 May, 2024

INTRODUCTION

The liver performs various physiological functions that ensure systemic homeostasis for optimum metabolic activities, growth and repairs[1,2]. The liver is also involved in biosynthesis of amino acids, bile and clotting factors[3]. Detoxification of drugs, xenobiotics, heavy metals, food toxins, toxins from pesticides, plastics, weedicides and food additives[4] are also undertaken by the liver. The liver is further responsible for the storage of glycogen and fat-soluble vitamins[5].

Hepatic disorders are conditions that alter the structure or functions of the liver resulting in alteration in its physiological activities[6,7]. They include hepatitis, cirrhosis, hepatocellular carcinoma, hepatoma, hepatosteatosis, jaundice, cholestatic injury, hepatobiliary obstruction, hepatovascular lesions and hepatozonal necrosis[8,9]. Hepatic diseases are caused by pathogens, toxins and environmental contaminants such as pesticides, weedicides, plastics, heavy metals and factory waste[10,11]. Abuse of alcohol, pharmaceutical drugs and food additives as well as iron overload also cause hepatic disorders[12-14].

Globally, 10% of the world population is living with various complications of hepatic disorders, leading to a million deaths yearly[15]. In Sub-Saharan Africa, 250 million persons are affected by various hepatic disorders whereas in Ghana, complications of hepatitis B and C alone account for 10,000 deaths yearly[16,17].

Serum markers of liver function and histopathological examination have been used to diagnose and characterize hepatic disorders[18]. Elevation in serum transaminases and bilirubin with low levels of proteins indicates parenchymal hepatic disease and hepatosteatosis[19]. Hepatobilliary and cholestatic conditions are characterized by high serum alkaline phosphatase (ALP) and gamma gutammyl transferase (GGT)[20-22]. Histopathological indications of nuclear pkynosis, cytoplasmic pigmentation and DNA fragmentation are features of hepatic necrosis[23].

Pathophysiology of liver diseases is centered on oxidative stress and synthesis of abnormal physiological proteins[23]. Oxidative stress results from overproduction of reactive oxygen, nitrogen and sulphate species from heavy metals, aflatoxin B1 and alcohol[24,25]. Consequently, these reactive species deplete glutathione stores and inhibit synthesis of free radicals scavenging enzymes such as catalase, glutathione peroxidase and superoxide dismutase[26,27]. Oxidative stress also activates the transcription factor nuclear factor-kappa beta (NF-kβ)[28]. Activated nuclear factor-kappa beta (NF-kβ) translocates from cytosol to nucleus where it causes continuous overexpression of proinflammatory and fibrogenic cytokines including tumor nuclear factor alpha (TNF-α), interleukin-6 (IL-6), transforming growth factor-beta (TGF-β) and epidermal growth factor (EGF)[29,30]. These pro-inflammatory cytokines result in sustained differentiation and proliferation of hepatic stellate cells into myoblast cells with collagen and muscle actins resulting in cirrhosis of the liver[31,32]. Cirrhosis obstructs blood flow to the liver resulting in hepatocyte hypoxia and necrosis[33]. In oxidative stress, transcription factors, sterol regulatory element binding protein-1c (SREPBP-1c), peroxisome proliferator-activated receptor-alpha (PPAR-α) and carnitine palmitoyl transferase-1 (CPT-1) are also overexpressed leading to hepatic lipogenesis, peroxidation and steatosis[34,35].

Pharmaceutical drugs have been the primary line of treatment for hepatic conditions in Ghana[36]. However, due to unavailability, cost and deleterious side effects, herbal medicines prepared from parts of medicinal plants have been used as alternatives[37,38]. The majority of plant-based Herbal Medical Practitioners (HMPs) in Ghana rely on folk knowledge and common daily experiences to select the choice of plant species and parts for preparation of medicines to treat hepatic diseases[39-41]. This study aimed to determine whether plant species used in preparing herbal medicinal products for the treatment of liver diseases have reported hepatoprotective activity.

MATERIALS AND METHODS

Study area: The study was carried out in Tamale in the Northern Region of Ghana, West African from June, 2020 to May, 2021. Some of the herbal products and sources of information were obtained in Accra, Wa and Kumasi all in Ghana.

Gathering of information on herbal products for liver diseases: In the field survey, information on herbal products and diseases was obtained from radio stations and television advertisements. Radio and station announcements and advertisements were followed and the medicines were recorded. Market surveillance and market van announcements were also followed.

Purchasing and verification of identified herbal products: The products were purchased from Tamale central, Bolga Central Market, Wa Central Markets and herbal stores. The inclusion criteria include Food and Drugs Authority (FDA) registration number, company batch number, not expired, plant species and parts that should be available and meant for liver disease. Exclusion criteria involve those not targeting any liver disease, expired, no batch or FDA number and plant species and parts not indicated. The products were verified from the FDA barcode and Traditional and Alternative Medicine Council logbook.

Extraction and compilation of plant species used for formulating the medicines: The plant species and parts used in manufacturing were extracted from the manufacturer's user instructions and the Traditional and Alternative Medicine Council logbook at Tamale Zonal Office.

Retrieving of articles for review from databases: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) instrument was adopted in conducting the review. Database search was conducted using plants' botanical names and parts and various hepatic diseases as keywords. Medline, PubMed, Google Scholar, Elsevier and Science Direct databases were searched. Inclusion criteria for the articles include the availability of the plant species, part used, extraction solvent and inducing model or toxin and from 2000-2022. Exclusion criteria include review papers, article published earlier than 2000 and research articles where the toxin, plant species, solvent, or liver diseases are not indicated. Quality of data on articles is assessed following the guidelines of JBI-MASTARI, Agency for Healthcare and Quality and Grading of recommendation, assessment, development and evaluation (GRADE).

Statistical analysis: Discrete data were reported as percentages and presented as bar charts. All entries were done using Microsoft Excel, 2016 version (Microsoft, Incorporated, New York). Analysis was done with Minitab version 17 (Lead Technologies Inc, New York). A p-value of 0.05 or less were deemed statistically significant.

RESULTS

Summary of number of articles used for the review: The number of articles downloaded and those eligible after meeting the inclusive criteria and quality checks are indicated in Table 1. In all, 250 articles were retrieved from the databases, but 175 met the inclusion criteria and quality checks and were used for the review.

Physical nature of the herbal products purchased: From the information provided by the manufacturers and Logbook of Alternative Medicinal Council, 56 plant species were used by 20 companies to formulate 25 herbal medicinal products against liver diseases as well as other illnesses. Of these, 17 (68%) were in liquid form while 4 (24%) were capsules. The powdered form was 8% while other forms such as charcoal and crude extract were also 2 (8%).

Frequency of each plant species among the herbal products: *Khaya senegalensis* was the most prevalent plant species used in formulating 9 different products followed by *Azadirachta indica*[7]. *Vernonia amygdalina*, *Moringa oleifera* and *Syzygium aromaticum* were found in 6 products whereas,

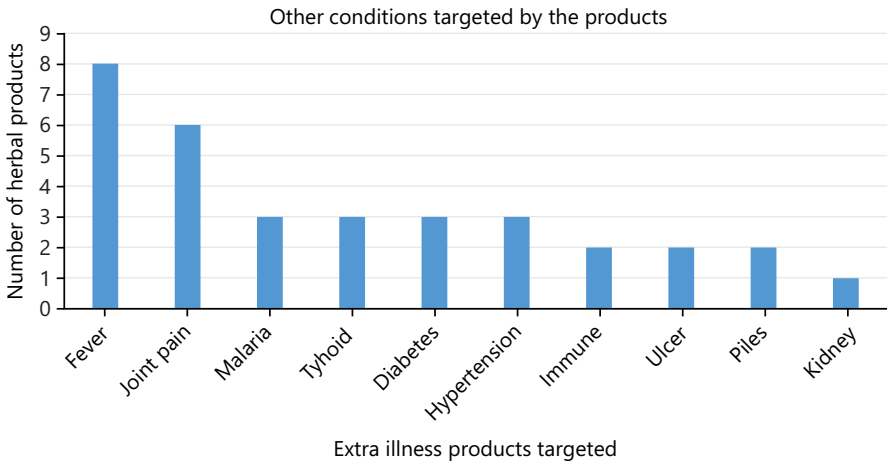

Fig. 1: Frequency of conditions herbal products were targeted

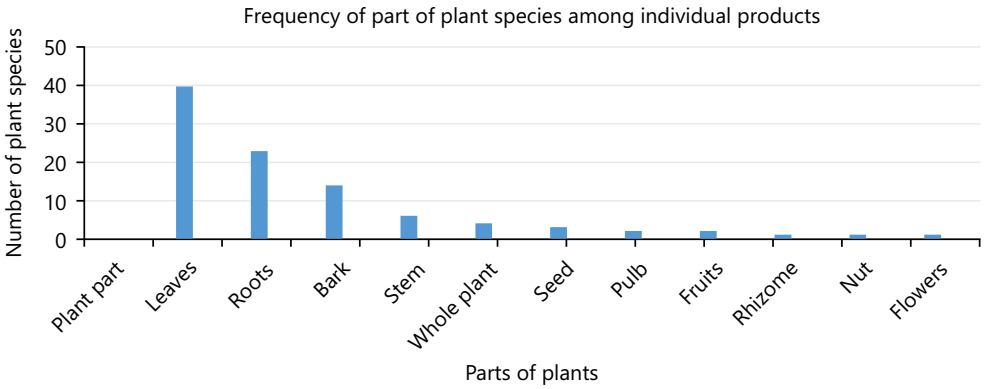

Fig. 2: Frequency of plant parts among the herbal medicinal products

Table 1: Articles used for the review of plant species

Article information	Number of articles
Articles downloaded from databases	250
Articles after removing duplications	225
Full text articles assessed for eligibility	189
Eligible records used for review	175

Curcuma longa, *Taraxacum officinale* and *Zingiber officinale* were found in 5 herbal products. *Allium sativum, Bidens pilosa, Trema orientalis, Piper guineense* and *Sida acuta* were each found in 4 products whereas, *Phyllanthus carolinianus* was used in manufacturing just 3 products. *Zingiber officinale*, *Vitellaria paradoxa*, *Trema orientalis* and *Acacia* spp., *Ageratum conyzoides*, *Allium cepa*, *Angophora hispida*, *Sida acuta*, *Ferruginea gigantea*, *Kigelia Africana* and *Tamarindus indica* were found in 2 products each while *Aloe barbadensis*, *Aloe vera*, *Alstonia boonei*, *Bombax buonopozense*, *Centella asiatica*, *Citrus aurantiifolia*, *Citrus lemon*, *Clausena anisata*, *Cola gigantea*, *Crataegus oxyacantha*, *Cucumis sativus*, *Eucalyptus globulus* and *Ficus exasperata* were each found in 1 product separately.

Diseases that herbal products were targeted in addition to liver diseases: Apart from liver-related diseases, herbal drugs were made for other sicknesses as presented in Fig. 1. Fever was the most frequent targeted by 8 (32%) products followed by joint pain 6 (24%) products. Malaria, typhoid and hypertension were each targeted by 3 (12%) products. About 2 (8%) products are made against immune disorders, ulcers and piles while 1(4%) product was made against kidney diseases.

Parts of the plants used to formulate the herbal products: Different parts of the same or different plant species were used in manufacturing a particular product. From Fig. 2, the majority of the plant species

Table 2: Plant species with data on hepatoprotective activity and those without data from the databases

Category	Plant species
Had hepatoprotective activity	*Crataegus oxyacantha*, *Tamarindus indica*, *Parkia biglobosa*, *Moringa oleifera*, *Sida acuta*, *Taraxacum officinale*, *Kigelia Africana* and *Syzygium aromaticum*
	Zanthoxylum zanthoxyloides, *Pericopsis laxiflora*, *Spathodea campanulata*, *Gentiana lutea*, *Citrus lemon*, *Azadirachta indica*, *Trema orientalis*, *Zingiber officinale* and *Piper guineense*
	Khaya senegalensis, *Momordica charantia*, *Mangifera indica*, *Ficus religiosa* and *Citrus aurantifolia*
	Aloe barbadensis, *Vitellaria paradoxa*, *Ficus exasperata*, *Paullinia pinnata*, *Solanum torvum*, *Vernonia conferta*, *Allium cepa*, *Cucumis sativus*, *Aspilia africana*, *Eucalyptus globulus*, *Hilleria latifolia*, *Ocimum gratissimum*, *Vernonia amygdalina*, *Allium sativum*, *Bidens Pilosa*, *Curcuma longa*, *Acacia* spp. and *Phyllanthus fraternus*
No hepatoprotective activity	*Nandea catifolien*, *Clausena anisata*, *Cola gigantea*, *Bombax buonopozense*, *Securindacalongi pedunculata*, *Paulinia acuminata*, *Alstonia boonei*, *Trichilia heudelotii*, *Panicum flavidum*, *Mondia whitei*, *Phyllanthus carolinum*, *Solanum erianthum*, *Angophora hispida*, *Ferruginea gigantea* and *Chrysophyllum africanum*

Table 3: Number of parts of each plant species reported

Plant species	Number of parts studied
Crataegus oxyacantha	7
Tamarindus indica	6
Parkia biglobosa and *Moringa oleifera*	5
Sida acuta, *Taraxacum officinale*, *Kigelia Africana* and *Syzygium aromaticum* *Zanthoxylum zanthoxyloides*, *Pericopsis laxiflora* and *Spathodea campanulata* *Gentiana lutea* and *Citrus lemon*	3
Azadirachta indica, *Trema orientalis*, *Zingiber officinale*, *Piper guineense* and *Khaya senegalensis*, *Momordica charantia*, *Mangifera indica*, *Ficus religiosa*, *Citrus aurantifolia*, *Aloe barbadensis*, *Vitellaria paradoxa, Ficus exasperata, Paullinia pinnata, Solanum torvum, Vernonia conferta* and *Allium cepa*	2
Cucumis sativus, *Aspilia africana*, *Eucalyptus globulus*, *Hilleria latifolia* and *Ocimum gratissimum, Vernonia amygdalina*, *Allium sativum*, *Bidens pilosa*, *Curcuma longa*, *Acacia* spp. and *Phyllanthus fraternus*	1

(40/56, 71.4%), leaves were used. This was followed by roots (23/56, 41.1%) plant species. Very few plant species (1/56, 1.8%) that their flowers, nuts and rhizomes were used to produce a product.

Categorization of the plant species, parts and diseases according to information from literature databases: On databases, 41/56 (73.2%) plant species had hepatoprotective activity while 15 (26.8%) had no data for hepatoprotective activity as indicated in Table 2.

Frequency of parts of the plant species reported: From data search, several parts of 41 plant species including leaves, bark, wood, root, seed, bud, flowers, fruits, fig, sap, twist were extracted with various organic and inorganic solvents and test against hepatotoxicity induced by various toxins. Table 3, indicates the number of parts of each plant species that was reported in scientific papers.

Types of extraction solvents used to extract plant parts: Various solvents including distilled water, ethanol, methanol, phenol, chloroform, petroleum ether and butanol were used to extract plant active components and indicated in Table 4.

Toxins used to induce liver diseases and tested against plant extracts: Various substances including carbon tetrachloride, paracetamol, tuberculosis drugs, etc. were used to induce liver disease in experimental models and then challenged with plant extracts. Table 5, indicates the number of different toxins that were used to induce liver disease in an experimental models and test against each plant.

Table 4: Number of different solvents used to extract parts of the plants

Plant species	Types of extraction solvents
Moringa oleifera	7
Momordica charantia and *Curcuma longa*	5
Tamarindus indica, *Parkia biglobosa*, *Sida acuta*, *Kigelia Africana* and *Syzygium aromaticum*	4
Zanthoxylum zanthoxyloides, *Gentiana lutea*, *Mangifera indica*, *Allium cepa*, *Ocimum gratissimum* and *Vernonia amygdalinam*	
Crataegus oxyacantha, *Spathodea campanulata*, *Citrus lemon*, *Zingiber officinale*, *Ficus religiosa*, *Ficus exasperata*, *Cucumis sativus*, *Allium sativum* and *Phyllanthus fraternus*	3
Bidens pilosa, *Aspilia africana*, *Eucalyptus globulus*, *Paullinia pinnata*, *Citrus aurantifolia*, *Mangifera indica*, *Solanum torvum*, *Piper guineense*, *Trema orientalis* and *Pericopsis laxiflora*,	2
Acacia spp, *Hilleria latifolia*, *Vernonia conferta*, *Aloe barbadensis*, *Vitellaria paradoxa*, *Khaya senegalensis* and *Taraxacum officinale*	1

Table 5: Number of different toxins used to induce liver diseases and challenged against plant extracts

Plant species	Number of inducing toxicants
Moringa oleifera	15
Curcuma longa	13
Zingiber officinale and *Allium cepa*	12
Azadirachta indica	10
Taraxacum officinale and *Syzygium aromaticum*	7
Ocimum gratissimum	6
Tamarindus indica, *Parkia biglobosa*, *Cucumis sativus*, *Vernonia amygdalina*, *Allium sativum*	5
Citrus lemon, *Momordica charantia* and *Eucalyptus globulus*	4
Acacia spp., *Solanum torvum*, *Mangifera indica*, *Spathodea campanulata*, *Kigelia Africana*, *Sida acuta* and *Crataegus oxyacantha*	3
Gentiana lutea, *Trema orientalis*, *Ficus religiosa*, *Citrus aurantifolia*, *Aloe barbadensis*, *Vitellaria paradoxa*, *Ficus exasperata*, *Paullinia pinnata*, *Bidens pilosa* and *Phyllanthus fraternus*	2
Hilleria latifolia, *Aspilia africana*, *Vernonia conferta*, *Piper guineense*, *Khaya senegalensis*, *Zanthoxylum zanthoxyloides* and *Pericopsis laxiflora*	1

Table 6: Comparison between frequency of plant species in herbal products and hepatoprotective activity in databases

		Number in reported scientifc data		
Plant species	Frequency in products	Parts	Extraction solvents	Inducing toxicans
Khaya senegalensis	9	2	1	1
Azadirachta indica	7	2	4	10
Vernonia amygdalina	6	1	4	5
Moringa oleifera	6	5	7	15
Syzygium aromaticum	6	3	4	7
Curcuma longa	5	1	5	13
Taraxacum officinale	5	3	1	7
Zingiber officinale	5	2	3	12
Allium sativum	4	1	3	5
Bidens pilosa	4	2	2	2
Trema orientalis	4	2	2	2
Piper guineense	4	2	2	1
Sida acuta	4	3	4	3
Crataegus oxyacantha	1	7	3	3
Tamarindus indica	2	6	4	5
Parkia biglobosa	1	5	4	5
Momordica charantia	1	2	5	4
Allium cepa	2	2	4	12
Ocimum gratissimum	1	1	4	6
Cucumis sativus	1	1	3	5

Comparison between frequency of plant usage and reported data on scientific reports: A comparison was made to determine if frequency of data on hepatoprotective activity of a plant species in terms of parts, extracting solvents and testing models determine its usage to formulate a herbal product and vice versa. There was no significant difference between the frequency of usage in a herbal product and that

of a number of parts as well as a number of extraction solvents reported. There was however significant difference between frequency usage in a product and number of toxins used in inducing models ($p = 0.017$).

DISCUSSION

Majority of the plant species (41/56, 73.2%) used in formulating the herbal products had data on the search engines in terms of parts, extracting solvents and inducing models. Whereas the products and the companies were wholly from Ghana, most of the journals reviewed were not published by Ghanaian Authors. This suggests that most of the plant species in Ghana have active components that can restore liver injury or companies and practitioners are relying on scientific information on the choice of plants for their medicines. This can also be attributed to the rapid upgrading of herbal medical practice in industry, academia and research. However, the level of herbal medicinal plants used for liver diseases is lower reported number of medicinal plants used for liver diseases in China, Korea and India[42]. van Quan *et al*.[41] reported that all the 300 plants used for liver treatment in Chinese traditional medicines have been test for hepatoxicity including hepatoxins. Jităreanu *et al*.[42] also reported that over 90% of 3000 medicinal plant species of Ancient Greek and Korea origins have been test for liver nutrients and toxins. Luo *et al*.[43] also reported that heavy metals and phytochemical screening has been achieved for all Taiwan medicinal plants. China, Korea and Taiwan have reported data on medicinal plants than Ghana due to the reliance on ancestral knowledge, superstition and lack of funding for scientific research in Ghana[44].

A greater number of the herbal products (17/25, 68.0%) were in the liquid form. Liquid phase of a product provides appropriate surface areas which increase the rate of absorption into the blood when ingested or injected. It also provides a large surface area for reaction with enzyme and other components for effective pharmacokinetics. Formulation of liquid of medicinal is also more cost-effective industrial process because it requires less effort, personnel and processes. Rubio *et al*.[45] also found leaves to be the predominant part of the medicinal plants used for herbal products.

Khaya senegalensis (Mahogany) was the most predominant plant used in formulating the herbal products. *Khaya senegalensis* is abundant in all parts of Ghana where it used as banks on roads, folder for ruminants and for building purposes. Herbal Medical Practice apart from health benefits, it's also an economic and industrial activity that depend heavily on the availability of raw plant materials. *Khaya senegalensis* has also been long used in Ghanaian ancient medicine to treat illness including jaundice. The abundance of *Khaya senegalensis* and its long use in folk medicine could account for its frequent use in the formulation of these products. Recent works by Ssenku *et al*.[46] found *Khaya senegalensis* as the most common plant species used for herbal medicinal products.

Leaves were also the most prevalent plant part used in the manufacturing of these herbal products. This could to attributed to the fact that leaves accumulate more synthetic plant nutrients, accumulate fewer plant toxins and are more conspicuous[46]. While the roots of the plants hold the plant firmly to the ground and absorb water, minerals and chemicals from the underground. The roots are likely to accumulate minerals, heavy metals and other chemicals from fertilizers. The leaves are responsible for excretion, photosynthesis and respiration and could accumulate metabolites and excretory products [46,47]which cause them to accumulate phytochemicals. Mbuni *et al*.[47] however found roots (35.9%), leaves (34.9%), bark (15.0%), fruits (5.2%), branches (5.0%), whole plant (1.9%) and flowers (1.1%) usage in herbal medicines in Western Uganda.

On the databases, *Crataegus oxyacantha* was most reported in terms of parts while *Moringa oleifera* was the most reported in terms of extracting solvents and inducing models. *Crategus oxycanthea* is comparatively more abundant and exists in more different and diverse parts than *Moringa oleifera*

and others. *Moringa oleifera* is one of the plants that has been used in ancient medicines to treat several illnesses. It is also used in various purposes such as ornamentals, drinks, oils, vegetables, salat, etc. da Silva *et al*.[48] found *Melissa officinalis* (31.0%), *Peumus boldus* (24.4%), *Mentha spicata* (20.9%), *Matricaria recutita L*. (18.2%), *Rosmarinus officinalis* (17.0%) and *Foeniculum vulgare* (14.7%) were the most used in a pool of 79 medicinal plants in Brazil. Mintah *et al*.[49] found *Azadirachta indica*, *Carica papaya*, *Mangifera indica*, *Moringa oleifera*, *Elaeis guineensis and Hibiscus sabdariffa* as the most common medicinal plant species used for herbal medicines for liver diseases in Southern Ghana.

Finally, there was a significance of difference between the frequency of usage in a herbal product and number of toxins used to induce a model for study. Scientific investigation of hepato-efficacy of a plant extract involves modelling the liver diseases in an organism or tissue and challenged with the plant extract. Whereas few parts of plants and solvents exist, there are over 65 substances that can be used to induce liver disease. Further, the nature of the toxin determines the kind of liver disease either acute, chronic, glandular, steatosis, parenchymal, hepato-biliary, or zonal that will be modelled. These toxins therefore influence the scientific investigation and reports which in turn influence the choice of the plant or part a practitioner or manufacturer chooses.

CONCLUSION

Majority of the herbal medicinal plants in Ghana have been tested against induced liver diseases and reported in the major scientific databases. *Khaya senegalensis* is the predominant plant used to manufacturing herbal medicinal products for treatment of liver diseases in Ghana. Further phytochemical screening, toxicity and testing in animal models are required to determine the safety and efficacy of the remaining plants without reported data in databases.

SIGNIFICANCE STATEMENT

The study provided data on the number and parts of herbal medicinal plants used for treatment of liver diseases in Ghana with and without reported hepatotoxicity in the major scientific databases. The study reveals majority of Ghana medicinal plants have been demonstrated against induced hepatotoxicity in various models. This forms basis for selection of candidate plant raw materials and further phytochemical and mechanisms studies.

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