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Comprehensive Research Overview on Some Hepatoprotective and Nephroprotective Medicinal Plants

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Abstract

Hepatic and renal diseases pose significant health challenges worldwide, necessitating the search for safe and effective therapeutic agents. Herbal medicine has received considerable attention recently after proving to be effective in many medical research. Hepatoprotective and nephroprotective properties of some herbs have garnered significant attention in recent years due to their potential in preventing and treating liver and kidney diseases. This comprehensive review summarizes and analyzes the previous scientific studies that have investigated the efficacy of various medicinal plants in protecting the liver and kidneys from damage. The primary objectives of this review are to compile existing research, assess the quality of studies, and identify promising medicinal plants for further investigations. A systematic search of scientific databases yielded a substantial number of studies that explored the hepatoprotective and nephroprotective properties of some medicinal plants. The review categorizes these studies based on the types of plant species used and the methodologies employed, offering insights into the diversity of approaches and outcomes. The findings from this review underscore the importance of continuing research in this area to better understand the potential therapeutic benefits of these medicinal plants. This knowledge may lead to the development of natural pharmaceutical agents that can effectively protect and enhance the function of the liver and kidneys, ultimately contributing to improved healthcare and the management of liver and kidney disorders.

Keywords: Hepatoprotective and Nephroprotective properties and Medicinal Plants.

Introduction

Liver and kidneys are the most essential and hardworking organs in the body. They carry out numerous vital functions. Liver is the largest solid organ in the body that performs over 500 vital functions, including the production of albumin and bile, detoxification of many substances such as drugs, filtering blood by removing toxins, byproducts, and other harmful substances, regulating blood sugar levels, storage of minerals and vitamins, regulating blood clotting and many other essential functions. The kidneys are two bean shaped organs, they are the body's filtration system. They play a key role in managing the body's fluid and electrolyte balance, one of their most important functions is detoxification and removing waste through urine. Liver and kidney disease are among the most prevalent and common worldwide medical issues, that pose challenges for healthcare professionals and pharmaceutical industry institutions because using conventional drugs has a negative and toxic effect on the liver and kidney tissues and may lead to liver damage **(Asrani, 2019)**. Recently, there has been a growing interest in using natural phytochemical compounds and discovering new drugs from medicinal plants as an alternative treatment in several conditions including hepatorenal disorders **(Sam, 2019).** Several studies were published with this concern and recommended this type of natural herbal medicine i.e (**Lü et al., 2010; Nyeem et al., 2017; Justin, 2018; Okaiyeto, et al., 2018; Ahd et al., 2019; Al-Sanai et al., 2019; Gehad, 2019; Ghalia, 2019 Hammad et al., 2019; Aya, 2020; Farzaei et al., 2020; Helmenstine, 2021; Mizzi et al., 2020; Ahmad et al., 2023; and Herbal medicine, medicalnewstoday.com).** The present review article was carried out to explore the results of more than fifty thesis and research papers studied these medicinal plants

Importance of medicinal plants

Plants have provided man with all his needs in terms of shelter, clothing, food, and fragrances **(Al-Asmari et al., 2014)**. Plants have formed the basis of traditional medicine practices since prehistoric times. Herbal medicine refers to plant-based substances used to treat illness and healing practices. These treatments consist of a complex mixture of natural compounds from various parts of plants, such as leaves, seeds, roots, fruits, flowers, bark, and stems known for their healing properties **(Medical News Today, 2022)**. Herbal medicines have many advantages where they are accessible and affordable, can be used as food and medicines. Recently, there has been a global trend to use medicinal plants in drug development. According to World Health Organization estimate in 1991, the herbal medicine market in european countries was about $6 billion, The global market of plant-based and plant-derived medicines was valued at USD 25.6 billion in 2015 with a compound annual growth rate of 6.6 % from 2015 to 2020 **(Roosta, 2017)**. The current annual global export value of the thousands of types of plants with medicinal properties was estimated to be $60 billion per year and growing at the rate of 6% per annum **(Wikipedia, 2024)**. Some herbal products may contain additives or other ingredients not listed on the label or be contaminated with other substances due to a lack of safety testing. According to data in 20countries (half

the population in many industrialized countries now regularly uses some form of traditional and complementary medicine (T&CM) (United States, 42%; Australia, 48%; France, 49%; Canada, 70%); considerable use of some form of T&CM exists in many other countries, such as Chile (71%), Colombia (40%) and up to 80% in some African countries **(WHO, 2023)**. Plants are important sources of medicines and presently about 25% of pharmaceutical prescriptions in the United States contain at least one plant-derived ingredient **(Verma, 2008)**. Furthermore, it is estimated that approximately 25% of modern drugs and as many as 60% of antitumor drugs are derived from natural products **(National Library Medicine, 2015; Taylor, 2017; Samani and Kopaei, 2018; Senosy et al., 2018; Sam, 2019 and Ur Rehman et al., 2021)**.

Conservation and sustainable use of medicinal plants

Medicinal plants are globally important sources of new drugs, in the United States, about 118 top prescription drugs are based on natural sources. the use of medicinal plants is proliferating due to increasing demand for herbal drugs and natural products **(Chen, 2016)**. According to the International Union for Conservation of Nature and the World Wildlife Fund about 50,000 - 80,000 plant species are used for medicinal purposes, about 15,000 of them are threatened with extinction from overharvesting and habitat destruction **(Chen, 2016)**. Therefore, it was necessary to study the conservation and sustainable use of medicinal plants on a large scale. There are many important recommendations related to their conservation, including conservation strategies and resource management techniques that reduce the depletion of medicinal plants, the development of good agricultural practices and sustainable use solutions through resource management technologies, as well as the creation of systems for inventorying species and monitoring their condition **(Raj, 2023)**.

Preparation of Medicinal Plants

The preparation and extraction of bioactive components of medicinal plants for experimental purposes is the first and key step in achieving quality research results. There are various methods used in the preparation and screening of medicinal plants in scientific research. The main stages to obtain a high-quality bioactive product from medicinal plants are the selection of a suitable solvent, extraction method, phytochemical screening procedures, fractionation methods and identification techniques **(Abubakar & Haque, 2020)**. The selection of these methods depends only on the design of the research. The choice of solvent depends on various factors such as type of plant, part of plant to be extracted, the polarity of the compounds, the nature of the plant material, the required purity of the extract, and the intended use of the final product. Some common solvents used for the extraction of medicinal plants are illustrated in Table 1.

Table 1. solvents and their extracted compounds.

Solvent	Polarity	The extracted compound
water	Polar (1.000)	Water soluble compounds such as polysaccharides, flavonoids, and tannins.
Ethanol	Polar (0.654)	Broad range of phytochemicals like alkaloids, phenolic compounds, and essential oil.
Methanol	Polar (0.762)	It is similar to ethanol but, it is more toxic and poses safety concerns, so its use is less common compared to ethanol.
Ethyl Acetate	moderately polar (0.228)	Polar compounds such as alkaloids, flavonoids, and glycosides.
Chloroform	Nonpolar (0.259)	Non-polar solvent that is effective for extracting lipophilic compounds such as terpenoids, fatty acids, and some alkaloids.
Aceton	Polar (0.355)	Effective for extracting a wide range of phytochemicals. It is mainly used in conjunction with other solvents as a solvent mixture.
Ether	Nonpolar (0.117)	Alkaloids, terpenoids, coumarins, and fatty acids.
Glycerin	Polar (0.812)	Non-toxic solvent used for extracting glycosides, mucilage, and other water-soluble compounds.

Different methods commonly used in the extraction of medicinal plants

1) **Maceration:** This is one of the simplest methods where a coarse powdered plant material, either leaves or stem bark or root bark, is soaked in a suitable solvent for a specific period to allow the extraction of bioactive compounds, then the solvent is filtered to obtain the extract.

2) **Infusion:** It is a simple process in which the drug material is ground into fine powder soaked in a suitable solvent like water, oil, or alcohol, and kept for a short time. This method is suitable for the extraction of bioactive constituents that are readily soluble (**Abubakar & Haque, 2020**).

3) **Digestion:** This method involves using moderate heat during the extraction process. The plant material is finely ground and mixed with the solvent, the mixture is placed over a water bath or in an oven at a temperature of about 50 C, and then the solution is filtered to remove solid particles.

4) **Percolation:** The apparatus used in this process is called a percolator. Dried and finely ground plant material is used and moistened with an extraction solvent. A large quantity of solvent is added, and the mixture is kept for a period of 4h. Subsequently, the contents are then transferred into a percolator with the lower end closed and allowed to stand for a period

of 24 hours. The solvent of extraction is then poured from the top until the drug material is completely saturated then the extract is separated by filtration **(Abubakar & Haque, 2020).**

5) **Soxhlet extraction:** This process is also known as continuous hot extraction. It is used for the extraction of delicate compounds that may degrade at high temperatures. The apparatus is called Soxhlet extractor made up of glass. A dried, ground and finely powdered plant material is placed inside a porous bag. The solvent is poured into the bottom flask heated, evaporates then condenses and flows down to the extraction chamber (**Abubakar & Haque, 2020**).

The recent methods in the extraction of medicinal plants

1) **Microwave-assisted extraction:** In this method, microwave irradiation is used to heat the solvent and speed up the extraction process. It is a fast and effective extraction technique. The disadvantage of this method is that it is suitable only for phenolic compounds and flavonoids.

2) **High-Performance Liquid Chromatography (HPLC):** it is an analytical technique used for separation, identification, and quantification of various components in complex mixtures It works by forcing a liquid sample through a column filled with a stationary phase (often silica) by a flowing mobile phase (liquid solvent) under high pressure, allowing fast and efficient separation of compounds based on their interactions with the stationary phase. When the compounds exit the column, they pass through a detector such as ultraviolet which measures the presence and concentration of each compound, Then analyze the data collected from the detector to identify and quantify the compounds present in the plant extract **(Mizzi, 2020)**.

3) **Ultrasound-assisted extraction:** This process involves the application of sound energy at a very high frequency greater than 20 KHz to disrupt plant cells and increase the drug surface area for solvent penetration this method is known for its shorter extraction times and higher extraction yields compared to traditional methods **(Abubakar & Haque, 2020).**

4) **Gas Chromatography (GC):** it ia an analytical technique used for analyzing volatile, semi-volatile and gasious compounds. This method does not extract compounds but is used to separate, identify, and quantify compounds extracted from plants.

Liver diseases and hepatoprotective medicinal plants

Liver diseases refer to conditions that damage the liver. It may develop for many reasons, including viral infection, alcohol overuse, long-term use of certain medications, exposure to toxins, or autoimmunity. According to WHO estimates, about 500 million people live with chronic hepatitis infection, it is the 11th leading cause of death and 15th leading cause of morbidity accounting for 2.2% of deaths in 2016 **(National Library Medicine, 2021)**.

Viral hepatitis is the inflammation of the liver caused by different types of viruses (hepatitis A, B, C, D, and E). Hepatitis C virus (HCV) infection is a major public health burden in Egypt, where it bears the highest prevalence rate in the world. In 2015,

Egypt's HCV infection prevalence of 7% among adults was among the highest in the world and accounted for 7.6% of the country's mortality **(Hassanin, 2021)**. Several medicinal plants exhibited high levels of antiviral activity.

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In a study by **(Arbab et al., 2017)**, 60 medicinal plants were collected, 57 from different regions of Saudi Arabia and 3 from Sudan. The plants were identified by a plant taxonomist at Faculty of Pharmacy, King Saud University. Dried plant materials were ground to a coarse powder, extracted with 80% ethanol for 3 days, followed by filtration and concentrated using a rotary evaporator under reduced pressure at 4°C. Cytotoxicity in the cell line (HepG2.2.15) was induced by 4, 5 - dimethylthiazole-2-YL and 2, 5 diphenyltetrazolium bromide (Mt). Twenty-four to forty-eight hours after treatment, the cells were visually monitored for morphological changes, such as cell membrane lesions and compaction of cytoplasmic components under a microscope. Analyses were performed further to investigate the antiviral potential of the active extracts of nine plants showed inhibition of HBsAg production in a dose-dependent manner. These plants were *Abutilon figarianum*, *Acacia oerfota*, *Capparis decidua, Coccinea grandis, Corallocarpus epigeus, Fumaria parviflora, Guiera senegalensis*, *Indigofera caerulea* and *Pulicaria crispa*.

Plants that exhibited anti-HBV activity showed the presence of alkaloids, flavonoids, tannins, saponins, and anthraquinones. Furthermore, **(El-Tantawy &Temraz, 2020)** made a review article to summaries the natural products which have a possible activity against HCV.

Hepatotoxicity is damage or injury caused to the liver due to exposure to harmful substances or medication. There are several medicinal plants that have potential hepatoprotective effects against hepatotoxicity, they are illustrated in Table 2.

Renal diseases and nephroprotecive medicinal plants

Recent statistics indicate that >10% of the general population worldwide suffers from chronic kidney diseases, accounting to >800 million individuals **(Kovesdy, 2022)**. In Egypt, recent statistics indicate that about 1 million Egyptians suffered from chronic kidney disease, including 50 thousand patients with kidney failure. The most common type of kidney disease is chronic kidney disease (CKD) which means the presence of kidney damage for a long term of at least three months and leads to gradual loss of kidney function which may end with kidney failure. Other common diseases include acute kidney injury, stones, infections, cysts, and cancer. Researchers are seeking to create alternative natural treatments for kidney disease

that are effective and have fewer side effects than conventional treatments and that in turn reduce the costs and frequency of dialysis. Table 3 illustrates some medicinal plants known to have nephron protection.

Table 2. Some medicinal plants with hepatoprotective potentials.

Name Of plant-compound	Family	Plant Parts Used	Used Extract	Dose (mg\kg)	Toxicity Inducing Agent	Parameters Studied	Reference
(*Combretum caffrum*) Combretastatin	Combretaceae	bark of the tree	ethanol 99.5%	1mg \ kg	CCL4	ALT, AST, ALP, Bilirubin oxidative stress markers GSH, SOD, MMP2, and histopathology.	(Hamza, 2019)
Gentiana lutea	Gentianaceae	root	70% ethanol	1 g/kg	ketoconazole	AFP, ALT, AST, and histopathology	(Hamza et al., 2023)
Curcuma longa	Zingiberaceae	rhizome	Methanol.	150, 300 and 600 mg/kg	CCl4	ALT, AST, ALP, total proteins, albumins, and histopathology	(Ibrahim et al., 2020)
Clutia abyssinica	Euphorbiaceae	Leaves	80% methanol	100, 200 and 400 mg/kg	CCl4	ALT, AST, ALP, TP, albumin, bilirubin, histopathologic.	(Meharie et al., 2020)
Neptunia prostrater	Mimosaceae	Whole plant	methanol and ethanol	200 mg/kg	CCL4	SGOT, SGPT, ALP and TB	(Jajo et al., 2021)
Balanites aegyptiaca (L.)	Zygophyllales	leaves	methanol	200 - 400 mg/kg	CCl4	SGOT, SGPT, ALP, TB, and histopathology.	(Ibrahim et al., 2016)
Terminalia arjuna	Combretaceae	fruit	Ethanol.	400 mg/Kg	Paracetamol	ALT, AST, ALP, LDH and histopathology.	(Moomin et al., 2020)
Allium sativum	Amaryllidaceae	bulbs	methanol	75 mg/kg	CCL4	ALT, ALP, SOD, GPx, GSH, TNF-α, CRP, and histopathology.	(Almatroodi et al., 2020)
Pandanus odoratissimus	Pandanaceae	seeds	methanol	300, 600 and 900 mg/kg	Paracetamol	GOT, GPT, ALP, and GGT.	(Almatroodi et al., 2021)

Table 3. Medicinal plants with Nephroprotective potentials.

Plant name	Family	Plant Parts Used	Used Extract	Dose (mg\k)	Toxicity Inducing Agent	Parameters Studied	Reference
Euphorbia geniculate	Euphorbiaceae	Aerial parts	70% methanol	200 mg/kg	TAA	CR, UR, SOD, CAT, GSH	(Al-Yousef et al., 2021)
Tilia cordata	Malvaceae	aerial parts	70% methanol	150-30mg/kg	cadmium chloride	creatinine, uric acid levels	(Fawzy et al., 2023)
Cymbopogon citratus (Lemon grass**) – Gum arabic**	Poaceae	stalks		360 mg/kg			(Said et al., 2019)
*Boswellia **sp.***	Burseraceae	bark	water	Drinking water (10% w/v).	paracetamol	urea, creatinine, PH (K+), (Na+), (Cl-), blood acidity (H+), (Ca+2) and (HCO3) ALT, AST, total bilirubin, urea, creatinine, and glucose CBC, PCV	(Mohamed et al., 2018)
Foeniculum vulgare (Fennel)	Apiaceae	seeds, leaves, and fruits	Diet supplement	--	Cyclosporine	Creatinine, ammonia, TGF-α1, TNF-α.	(Süzek and Dogan, 2017)
Ceratonia siliqua L. (Carob)	Fabaceae	pulp					
Hyphaene thebaica	Arecaceae	Fruit, pulp					
Terminalia ivorensis	Combretaceae	stem bark	Ethanol (70%)	300-1000 mg/kg	Potassium dichromate	GSH, SOD, catalase levels, and Histopathology.	(Moomin, et.al., 2020)

Oxidative stress and antioxidants

Free radicals are highly reactive molecules that contain one or more single electrons. They are produced naturally in the body as byproducts of metabolic processes, or from external sources such as pollution, cigarette smoke, radiation, and medication. When an imbalance occurs between the generation of reactive oxygen molecules and the body's antioxidant defense capacity leads to the accumulation of free radicals and causes a phenomenon known as oxidative stress which plays an important role in the development of pathological conditions for the liver and kidney **(Pizzino, 2017)**. Free radicals can accumulate in the liver and kidneys, leading to inflammation, cell damage, and impaired their function. Antioxidants are compounds that neutralize free radicals and scavenge them from the body. The body can produce its own antioxidants, and we can also obtain them from natural sources such as: fruits, vegetables, nuts, and medicinal plants. In the scope of many research, the investigation of a plant-origin antioxidant is essential for the development of potential therapies for liver and kidney disorders. By studying the antioxidant properties of medicinal plants, researchers aim to reduce oxidative stress, and inflammation, and improve the health

of these organs, offering new treatment options for individuals suffering from liver and kidney conditions**.** Table 4 illustrates the common natural antioxidants **(Akbarirad, 2016).**

Table 4. Most common natural antioxidants and their sources.

Phytonutrient compounds	Natural source
Polyphenol	Cloves, Star Anise, Cocoa Powder, Dark Chocolate, flaxseed, coffee, and tea.
Anthocyanin	Raspberries, eggplants, carrots.
Resveratrol	Dark Chocolate, Peanuts, grapes
Lycopene	Pink grapefruit, watermelon, red pepper, tomato
Lutein	Spinach, broccoli, lettuce, kale, artichokes, cabbage.
Ascorbic Acid	Citrus fruits
Polyphenols	Green tea, blue berry, black berry, concord grape, red cabbage.

Hepatorenal protective medicinal plants

The liver and kidney have a complex relationship. Functional renal failure is a common complication with liver disease, therefore, there are some researchers who have conducted scientific papers that studied herbal plants having potential hepatoprotective and nephroprotective effects (Table 5).

Side effects of some medicinal plants

Though herbal remedies are derived from plants, it's important to remember that "natural" doesn't necessarily mean "safe". Some herbs may cause negative side effects, and some herb mixture may cause conflict with some pharmaceutical drugs. Previous studies indicated that some herbal supplements potentially interfere with blood clotting as their antiplatelet effects are mediated by inhibition of formation, release, aggregation, or platelet activation (**Abebe, 2019**). Some of the common herbal supplements with antiplatelet properties are:

Aloe *(Aloe vera*), Ginger (*Zingiber officinale*), Garlic (*Allium sativum*) Cranberry (*Vaccinium macrocarpon*), and Ginkgo (*Ginkgo biloba L*.). **(Abebe, 2019).** Studies also proven that some herbs have anticoagulant effects, as they contain coumarins which blocks the action of vitamin K and interfere with clotting factors e.g.: German Chamomile *(Matricaria chamomila*) Red clover (*Trifolium pretense*), and Fenugreek (*Trigonella foenum graecum*). *Ginseng* also interferes with diabetes and hemophilia drugs. In addition, it should be noted that the treatment period of medicinal plants is usually longer compared to traditional medicines (**Abebe, 2019)**.

Table 5. Medicinal plants with both Hepatoprotective and Nephroprotective potentials.

Plant Name	Family	Plant Parts Used	Used Extract	Dose (mg\k)	Toxicity Inducing Agent	Parameters Studied	Reference
Gazania rigens	Asteraceae	whole plants	95% ethanol	300 mg/kg	CCl4	AST), TB, creatinine, urea, albumin, TG, cholesterol, LDH.	(Gomaa et al., 2022)
Origanum Majorana (Sweet Marjoram)	Lamiaceae	leaves	distilled water	200 mg/kg	Ivermectin	AST, ALT, ALP, total bilirubin, TG,cholesterol, Albumin, TP, Globulin level, (HDL, LDL, serum urea, creatinine, Potassium, and sodium serum level.	Elmahdy and Alkalamawy, 2022
Argania spinosa L. (Argan oil)	Sapotaceae	Seeds	Seeds oil	2 mL/Kg	CCl4	ALT, AST, total and direct bilirubin, TG, LDL, creatinine, urea, uric acid, and MDA levels.	(Mohamed et al., 2021)
(Curcuma longa) (Turmeric)	Zingiberaceae	rhizomes	water	100 mg/kg	RIFAMPICIN AND ISONIAZID	AST, ALT, ALP, bilirubin, blood urea, and creatinine	(Thuawaini et al., 2019)
Annona muricata	Annonaceae	Leaves and fruit	70% ethanol	200 mg/kg	Ehrlich ascites carcinoma cells	LDH, MDA, TAC, GSH, SOD, CAT, and Histopathology.	(Hassan et al., 2019)
Passiflora Sp. Passion Fruit	Passifloraceae	peel	Ethanol 250 mg of purple passion 500 mg of red passion fruit 500mg of yellow passion fruit		Paracetamol gentamicin	ALT, AST, urea, and creatinine serum levels.	(Nerday and Ritarwan, 2019).

Conclusion

Medicinal plants used in traditional medicine are rich sources of active medical components such as phenols, coumarins, lignans, terpenoids, carotenoids, glycosides, flavonoids, organic acids, alkaloids and xanthines. Numerous research conducted on various animal models (in vivo and in vitro models) has proved that extracts of some medicinal plants possess potential hepatoprotective and nephroprotective activity .The data of this review can serve as a basis for the search of the best and most effective varieties of medicinal plants for the development of dietary supplements and pharmaceuticals used for the protection and treatment of hepatorenal diseases. Further studies are needed on these plants to explore their efficacy and safety through controlled clinical trials, and there should be an incentive plan for the research center of medicinal plants to establish cooperative research activities between the relevant institutions.

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