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A Systematic Review on Nephroprotective Plants

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A B S T R A C T

Nephrotoxicity occurs when the body is exposed to medicine or toxin, which is one of the most prevalent kidney diseases. There are various numbers of therapeutic agents responsible for the occurrence of nephrotoxicity like anticancer drugs, antibiotics, some NSAIDs, etc. These agents weaken kidney function which results in renal failure. Nephrotoxicity is the poisonous effect of some substances that may include both toxic chemicals and medication on the kidney. Many medicinal herbs, natural compounds, and dietary components have been studied as possible nephroprotective agents. This article represents the review of different kinds of nephroprotective agents. Medicinal plantsplaya major role as a source of potential compounds for the development of effective therapy for the treatment of kidney problems. Many kinds of literature searches have been done and proved that; many medicinal plants have nephroprotective activity. Herbal medicines possess curative properties due to the presence of phytochemical constituents. The review represented all the details of phytochemical constituents of a medicinalplant which are used as nephroprotective drugs

Keywords: Nephroprotective, Kidney Disease, Renal Failure, Medicinal Herbs, Phytochemical Drugs

1. INTRODUCTION

In the human body,the kidney is the most vital organ and is involved in the excretion of metabolic substances and toxic waste from the body and is also involved in the metabolism of carbohydrates, protein, lipids, and other nutrients. The main mechanism is tubular cells which are responsible for the generation of glucose through gluconeogenesis. Many times humansare exposed to some toxic conditions and toxic agents in the environment or many different physiological conditions like metabolizing activity, increased concentration of chemicals filtered in the tubular fluid, and heavy blood flow to the organ leads to high vulnerability towards toxins. Due to this toxicity effectof medicines and other agents,there is a rapid deterioration in kidney functionwhich is called nephrotoxicity. The detrimental effect of chemicals on renal function is known as nephrotoxicity.Different mechanisms cause nephrotoxicity which includes renal tubular toxicity, glomerular damage, crystal nephropathy,and inflammation**[1-5].**The different substances responsible for nephrotoxicity includemolds and fungi, cancer-causing agents like cisplatin, antibiotics like aminoglycosides, metals which include lead, arsenic, mercury. Renal failure may cause due to intrinsic and extrinsic. Cardiovascular disease, obesity, diabetes, sepsis, lung failure, and liver failure are the extrinsic factors whereas intrinsic factors are related to kidney function which includes kidney disease like, glomerular nephritis, polycystic kidney disease, tubular cell death, and stones**[6-8]**.

The diagnosis and characterization of the kidney disease have come under renal pathology and these are non-tumor related. Renal pathology and nephrotoxicity are distinguished when the kidney is not infected by drug-induced damage. There are many common things in between renal pathology and nephrotoxicity like both are caused due to the damaging of renal cells or renal cell death which causes changes in the structural and functional unit of the kidney which are called nephrons. It is represented in figure 1. The changes in kidney cells include glomeruli, interstitium, tubules, and renal blood vessels**[9, 10].** Millions of nephrons are available in the typical kidney structure and its main function is to filter the waste material from the body and overall maintenance of fluid balance in the body, maintenance of pH of blood, and hormones which are responsible for promoting red blood cells production. It also regulates bone health and regulated blood pressure. Nephrotoxicants are mainly responsible for damaging the renal cells. Kidney damage characterization and its staging are also similar only in case damage is caused due to Nephrotoxicants and renal pathology**[11, 12].**

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Nephrotoxic agents

When the human body is getting exposed to harmful drugs and industrial and environmental chemicals then it may cause renal disease or dysfunction of the kidney may occur. The kidney has an excretory function and hence it becomes very susceptible to the effects of environmental toxins and these toxins damage the kidney and increase the level of electrolytes in the blood. These electrolytes include potassium and magnesium and make them unable to eliminate extra urine and wastes from their bodies**[13, 14]**There are various exogenous and endogenous toxic agents like illegal abortifacient, anticancer drugs, antibiotics, and heavy metal which are used for long exposure. All these agents are responsible for the manifestation of the disease. There different groups of nephrotoxic agents like metals, non-steroidalanti-inflammatory drugs (NSAIDs), solvents, glycols, anticancer drugs aminoglycosides, and antibiotics, etc. Metals include mercury ad its vapors which causes the necrosis of proximal tubular cells of the kidney. Bismuth causes dysfunction and necrosis of kidney cells. Thallium, gold, Barium, Potassium are the metalsthat are responsible for causing the cell death of the kidney. Barium causes potassium inhibition from the cells and hence results inhypokalaemia. In NSAIDs ibuprofen, aspirin, indomethacin are responsible for interstitial nephritis and also causes acute renal failure, retention of potassium, and also hypertension.

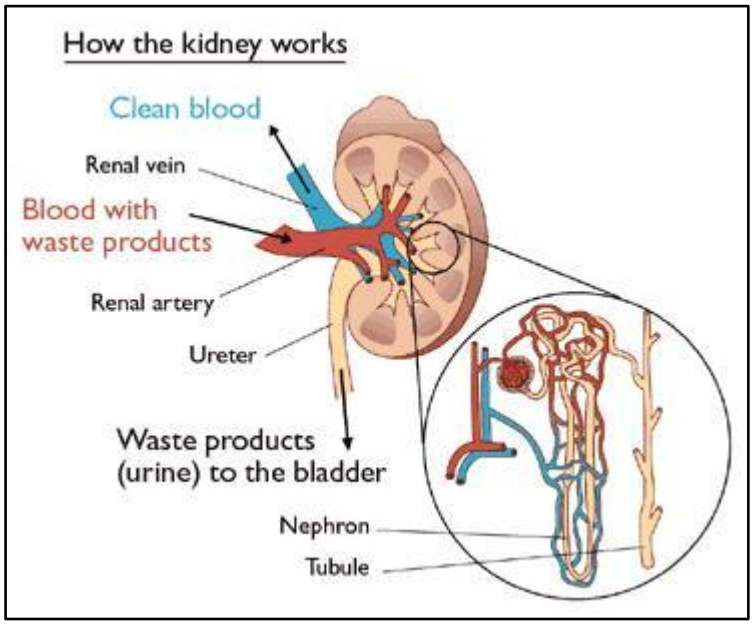


Figure 1: Structure of kidney

Major solvents involve carbon tetrachloride (CCl4), toluene, and tetrachloroethylene. Conversion of the CCl4 forms the free radicals of trichloromethyl and trichloromethylperoxyl. Free radicles always causing damage to the cells and hence renal cells get damaged by these free radicals. Formation of renal tubular injury andnecrosis hypertension produced. Poisoning of tetrachloroethylene leads to acute renal failure from tubular necrosis. Calcium oxalate crystals are formed from the ethylene glycol by the formation of the glycolic acid and oxalic acid and its crystals get deposited into the renal tubules hence results in hindrance and results in renal failure. Due to the formation of crystals, it can cause the inflammation of the interstitial which results in fatal hematuria, proteinuria, oliguria, or anuria. Anticancer drugs include different classes of drug-like alkylating agents, antimetabolites, radiocontrastagents, and antitumor antibiotics. Cisplatin is a very potent alkylating agent and causes severe nephrotoxicity and hence its use is limited. It decreases the level of anti-oxidant enzymes and hence increases the production of reactive oxygen species metabolites and peroxidation. Various aminoglycosides like streptomycin, gentamicin, and amikacin are used tremendously in the treatment of gram-positive and gram-negativebacterial infections. However,these drugs cause nephrotoxicity hence they have major limitations in clinical use. Gentamicin is responsible for the production of reactive oxygen species and hence causing renal failure. Certain antimicrobial agents like acyclovir, tetracycline, sulfadiazine, and rifampicin**[15-18].**

Nephrotoxicity which is induced by the drug can be categorized into the three stages like initiation phase in which toxic material is get interacted with the molecules like lipid, protein, DNA, RNA, and inactivates them. By this inactivation, these molecules tend to form ROS and free radicals and it produces a strong effect on the semipermeable membrane.The second stage is the propagation phase, where it is an irreversible phase and toxicants interrupt the major pathways. The third stage is termination phase in which toxins causes the cell necrosis, it destructs the cell membrane and all cells content burst, ultimately causing kidney damage**[19,20].**

Different factors are associated with renal injury. For example, many drugs causing renal damage by different mechanisms with the help of direct cell toxicity or due to high doses of the drugs. Eg.Aminoglycosides and amphotericin B, due to excessive use of these drugs patients may suffer the risk conditions. Some drug saturated into the renal tubules and hence causes the lysosomal dysfunction and hence cell swelling**[21, 22].** Patient-specific factors are also increasing the risk of nephrotoxicity induced by the drugs. In females, body mass is different than male and reduced total body water from the female will leads to the highest chances of nephrotoxicity. Genetic alterations in the human immune system can lead to producing inflammatory injury and thereby increases the risk of nephrotoxicity. Patients having liver disease, heart disease, or any metabolic disorder are also the major risk factor to increase the risk of nephrotoxicity. The kidney itself is the major risk factor if the high rate of blood flow and more cellular activitycan cause the kidney to make it susceptibleto nephrotoxicity**[23, 24].**

1. Nephroprotective drugs

Traditional drugs are very valuable in primary healthcare needs. As per WHO, more than 80% of the population is using traditional medicineswhich provides complete health benefits, especially in developing countries**.** These are the vital source of the useful potential new compounds used in the development of the different therapies.Traditional functional drugs act as a powerful preventative against a variety of ailments. Consumption of such herbs contains bioactive components and which has been advised in several studies. These herbs have medicinal values and protect against diseases. The plant sources which are used in the therapy or development of effective therapy in different kinds of kidney problems are known as nephroprotective drugs**. [25-27].**The desire for safer and less expensive plant-based therapies has risen in response to the problem of growing resistance and adverse effects from pharmaceutical medications. Nowadays, herbal formulation awareness has been increased tremendously and patients have been getting forced to take medications along with natural medicines. This may create undesired effects due to the interaction between drugs and herbal drugs**[28].**Medicinal plants like herbs and form different parts of the plants consist of different variety of phytochemical constituents like alkaloids, glycosides, carotenoids, different phenolic compounds which has the antioxidant property. These plants are regarded as a healthy alternative for treating oxidative stress-related illnesses and can thus be utilized to treat a variety of renal ailments due to their therapeutic characteristics. Traditional knowledge will act as a powerful search engine, and will, more significantly, considerably facilitate intentionally, focused, and safe natural product research to rediscover the drug discovery process.**[29, 30].**

Phytoconstituents from different medicinal plants as nephroprotective:

Artemisia annua

In China, this is known as Qinghaosu. *Artemisia annua* (Asteraceae) is a green herb and it has been used for protozoal infection. It is an antimalarial drug. Traditionally it was used in the treatment of fever and hemorrhoids. It has been proved in the infection against *Plasmodium falciparum* malaria and currently it is available in the formulation like intrarenal, rectal and oral. Its ethanol extract is proven to be nephroprotective and it is due to the terpenoids present in it. These terpenoids include Artemisia ketone, α-pinene**[31, 32]**it is also knownas the sweet wormwood, its extract from the crude drug is a good source of artemisinin and this is the natural sesquiterpene. Sweet wormwood is also a good source of essential oil and is used in the fragrance industry. Leaves of these plants consist of more amounts of flavonoids and which is having antiviral and antioxidant activity**[33-35].**

Curcuma xanthorrhiza.

It is widely distributed in the Java islands of Indonesia, Malaysia, and Thailand and also in China. Its common name is "Java Ginger". *Curcuma xanthorrhiza*consists of the xanthorrhizol which is sesquiterpene and it is antibacterial, anticancer, and anti-inflammatory. The stem part of the plant is used in the treatment of inflammation in postpartum urine bleeding. Kim SH et al 2005 has been studied and proved it has nephroprotective activity**[36].**

Zingiber officinale

It is most commonly known as ginger and has been using as a medical plant in many countries. *Zingiber officinale, (Zingiberaceae)* is the major source of gingerol due to which ginger is pungent in taste. It consists of homologous phenols. Its action is reported as an antiemetic, spasmolytic, carminative, anti-inflammatory, and peripheral circulatory stimulant. Aqueous and ethanolic extracts of ginger are effective against cancer and it is used in the doxorubicin-induced nephrotoxicity. **[30]**

Aervalanata

Aervalanata (Amaranthaceae) is distributed in all over India which is known as a common weed in tropical India. It is also found in Africa, ShiLanka, and the Philippines. Its use in medicine is diuretic, anthelmintic, and also an expectorant. The leaves of the plants are used in the treatment of diarrhea and kidney stone. Its root is used in the treatment of snakebite. This plant has many advantages and is used in the hemorrhage during pregnancy, many skin diseases, headache and also to dissolve the kidney stone and gall bladder stone. It is employed for uterus clearance. The major constituent of this plant is flavonol glycoside which consists of Kaempferol and its derivatives kaempferol-3-rhamnoside and kaempferol-3-rhamnogalactoside which are considered as the promising role in nephritic injury and kidney damage caused due to nephrotoxicity. It is mainly used in nephrotoxicity induced due to cisplatin and antibiotics**[37, 38].**

Curcuma longa

*Curcuma longa*is belonging to the family Zingiberaceae as that of ginger. It is most commonly known as turmeric. It is most widely found in India, China, and other different countries of tropical climate. Curcumin is the main chemical constituent of this plant and it is widely used in various diseases. It is used as an antibacterial. Dried *Curcuma longa* is a part of the spices used in Indian culture. Curcuminoid are desmethoxycurcumin and bisdesmethoxycurcumin. These are the polyphenols and give the yellow color to the turmeric. It is used in spices, dyes, flavoringagents, coloring agents, etc.It is used in the treatment of jaundice, hemorrhage, and in colic. It has anti-oxidant, anti-inflammatory property**[31, 39]**

Andrographis paniculata

*Andrographis paniculata*which belongs to the family Acanthaceae and it is well known as 'king of bitters. Mostly it is cultivated in southern Asia. Its part of the plant used is leaves and roots and is widely used in different ailments. The main chemical constituent of it is diterpenoid andrographolide and stigmasterol.It is used in cancer treatment, heart disease treatment, and also in diarrhea. It has anti-inflammatory activity and also hepatoprotective. The chloroform extract of *Andrographis paniculata* is effective against nephrotoxicity due to the presence of andrographolide and diterpenoids in it**[40].**

Berberis vulgaris

Berberis vulgaris belongs to the family Berberidaceae. It is mostly found in southern Europe and western Asia. This drug was extensively used in ancient times as a medicinal plant in the treatment of various diseases. It consists of organic acids and phenol compounds. It also contains anthocyanin and antioxidant pigment and glycoside enzymes. Roots are the part of the plant used and which consist of berbamin and iso-kaolin alkaloid. It has strong antioxidant, anticancer, antipruritic, antiemetic properties. It has cholagogue actions and it is also used in the treatment of jaundice, dysentery, in malaria. Berberis vulgaris has nephroprotective activity due to the presence of berberine alkaloids**[31, 41].**

Camellia sinensis

Camellia sinensis is belonging to the family Theaceae. It is the tea plant and is mostly observed as black, green, and oolong tea. This drug is native to China and also found in India, Southeast Asia. It is cultivated all over the planet in the tropical region. Flavonols and catechins are chemical constituents. Epicatechin, epicatechin-3-gallate, epigallocatechin, and epigallocatechin-3-gallate are the main catechins found in green tea. This plant is used in the treatment of cancer and also acts as an anti-inflammatory, probiotic,and antibiotic. Catechin has been proved as protective against nephrotoxicity**[42].**

Ceratonia siliqua

Ceratonia siliqua belongs to the family Leguminosae which is found in Mediterranean climates and grows very well in hot and humid coastal regions. The main chemical constituent is carob polyphenols and tannins. Tannins thatare extracted from the pulp give the antidiarrheal action. Carob bean has many applications in the cosmetic industry. Carob polyphenols are the important phytochemical constituent that has the defensive mechanism in nephrotoxicity**[31].**

Nigella sativa

Nigella sativa having the family Ranunculaceae which is mostly found in the Syrian Arab Republic, Israel, and southern Europe. The seeds of these plants and their oil are very important and used in many diseases. These seeds are very bitter and act as appetizers, diuretic and carminative. It has a deodorant, purgative and expectorant action. The oil acts as an anesthetic. Active chemical constituents present in this plant are, Thymoquinone, Thymohydroquinone, t-anethol, sesquiterpene. Thymoquinone is a phytoconstituent found in Nigella sativa that plays a crucial role in the plant's health. in the treatment of gentamicin-induced toxicity to the kidneys **[43].**

Panax ginseng

Panax ginseng belongs to the familyAraliaceae. It is all over East Asia and Russia. It is most widely cultivated in different regions of Asia. In Japan, China, and Korea, the plant is used as a medicinal herb. It is a perennial plant and having five-fingered leaves. Triterpenes, glycosides, ginsenosides are the main chemical constituents. It is having anticancer activity, it regulates the blood sugar level, fatigue, and immunomodulation in human health. Ginsenoside Rh3 and Rh4 are having nephroprotective activity against cisplatin-induced nephrotoxicity**[44].**

Cordyceps cicadae

*Cordyceps cicadae*which is the ascomycetes fungus belonging to the family Clavicipitacea. It is mostly found at a high altitude hence its harvesting is quite difficult. Being such difficulties, this is one of the most expensive drugs amongst other medicines. In ancient times, it was used in many different ailments like kidney disease, heart disease, dysfunction of male and female sexual health, etc. Cordycepin and its derivatives, and ergosterol, polysaccharides, and glycoprotein are the main chemical constituents of this plant, also, it consists of the alfa aminobutyric acid. It has many different pharmacological activities like antiarrhythmic, antimicrobial, insecticidal, anti-aging, neuroprotective, and renoprotective. The main sterol which is ergosterol having nephroprotective activity **[45].**

Picrorhizakurroa

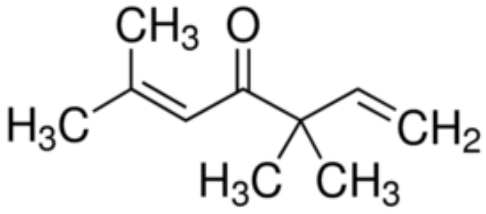
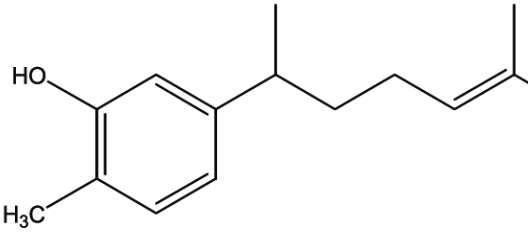
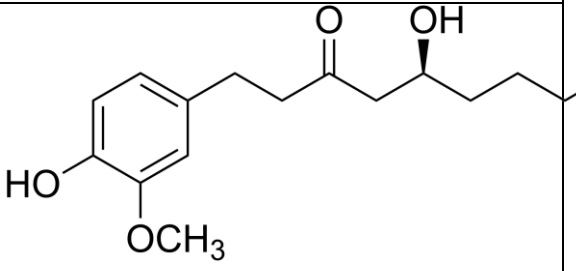
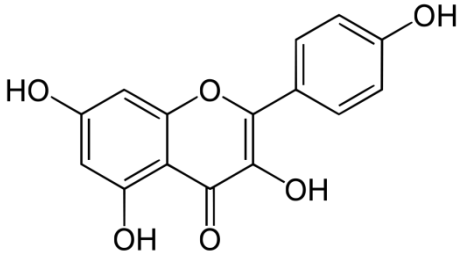
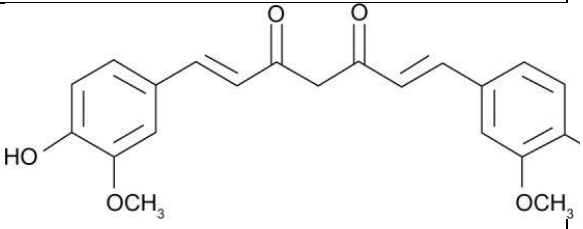
*Picrorhizakurroa*which is having the family' scophulariaaceae. It is cultivated in northeast India on the slope of the Himalayas. It is also found in Tibet and China. Traditionally it was used in the scorpion sting and also in bronchial problems, dyspepsia, and dysentery.Kutkoside and picroside are the major chemical constituents in this plant. PicrosideI, II, and III are the different compounds. These are having hepatoprotective activity, antioxidant and immune-modulating activity. The major chemical constituents that meankutkoside and picrosidewhich are present in this plant are having nephroprotective activity **[46].**

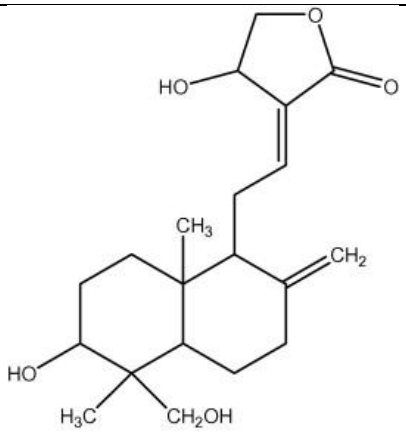
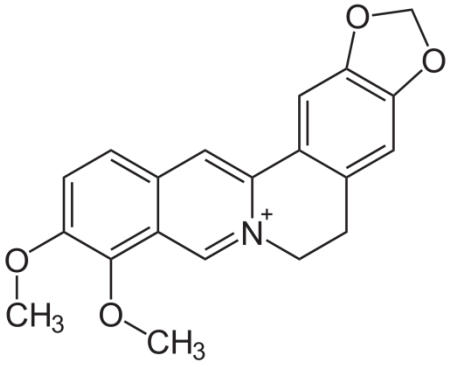
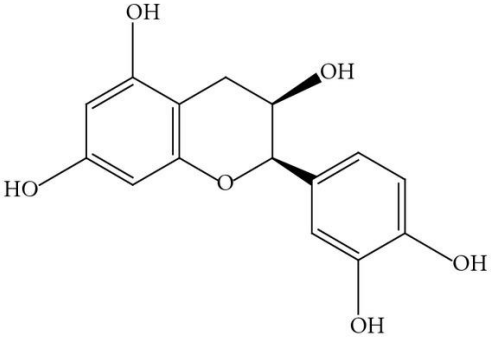
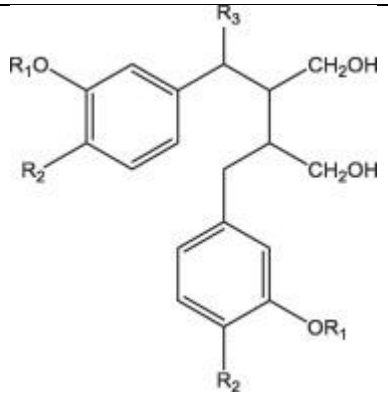
Many medicinal plantspossess nephroprotective activity against drug-induced nephrotoxicity. Such examples with their biological source and major constituents along with structures have been represented in table no 1**[31]**

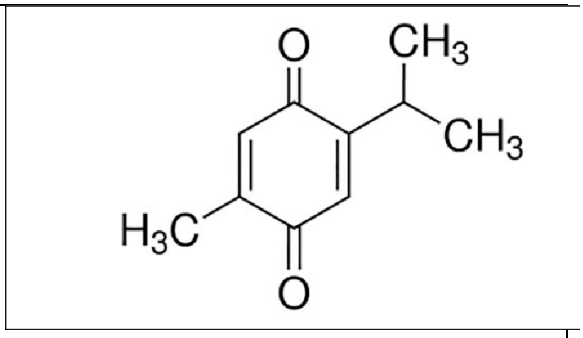
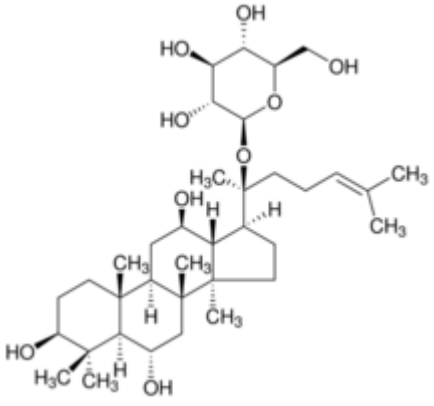
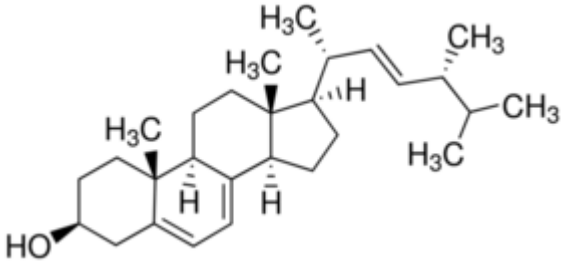
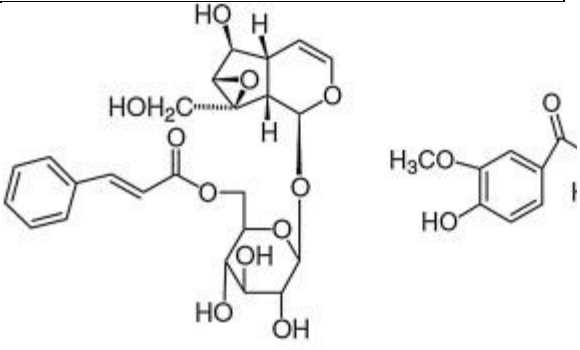
2. LITERATURE REVIEW

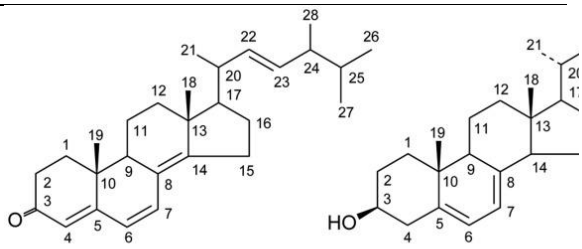
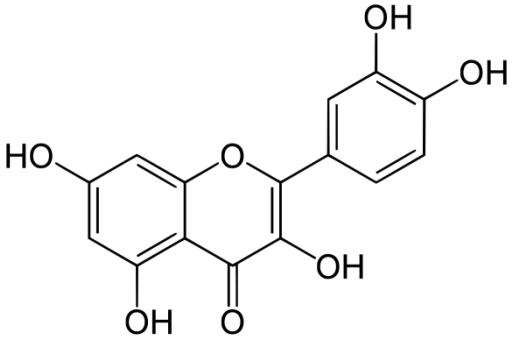
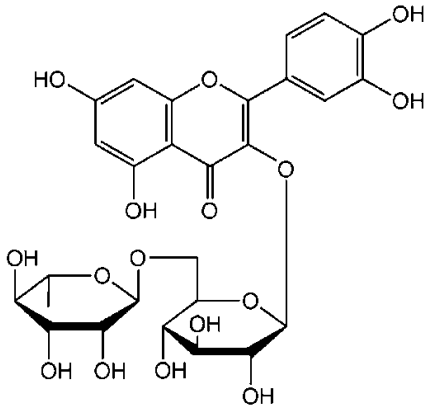
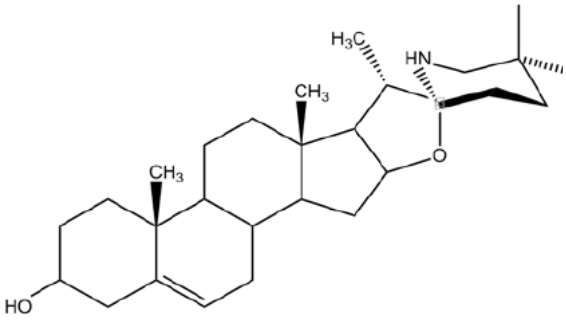
Venkatesan N et al; 2009, studied the nephroprotective activity of curcumin in rats. The study investigated Adriamycin (ADR) induced nephrotoxicity. In the study, it was found that ADR-induced kidney which was damaged was prevented by the use of curcumin. The study also demonstrated that curcumin also prevents oxidative stress and increases the glutathione content and increases the activity. Curcumin was found to be the providing approach in nephrotoxicity**[39]. Rao NK et al; 2006,** studied the effect of*Andrographis paniculata*rootsin renal diseases. Chloroform extract of these roots was tested for anti-hyperglycemic activity in alloxan-induced diabetic rats. The study was demonstrated the significant antidiabetic activity with chloroform extract. This extract was also useful in the prevention of diabetic nephropathy**[40]. Jyothilakshmi V et al; 2013,** investigated the action of*Berberis vulgaris* in the treatment of renal calculi, where they focused on the potential activity of root bark of *Berberis vulgaris* which is very commonly used in homeopathic treatment. Urolithiasis was induced first in rats and then a study was done. It was found that stone-forming constituents were getting normal due to the use of *Berberis vulgaris*. Serum creatinine levels were also got normal. It was concluded that *Berberis vulgaris* was effectively shown the action against renal calculi**[41].Baek SH et al; 2006,** studied the effect of ginsenoside in the reduction of cisplatin-induced nephrotoxicity which was done on cultured renal tubular cells. It was observed that Ginsenosides Rh4 and Rh3 increased the cell viability in a dose-dependent manner. However,the cytoprotective mechanism was unclear but needs to study further**[44].Özen S et al; 2004**investigated the effect of caffeic acid phenethyl ester in nephrotoxicity induced due to cisplatin in the rats and it was found that caffeic acid and phenethyl ester showed the action against cisplatin-induced antioxidants. There was a marked reduction of tubular damage**[47].**

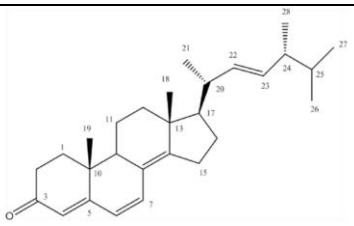
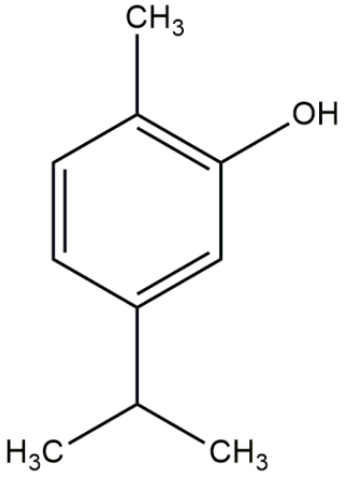
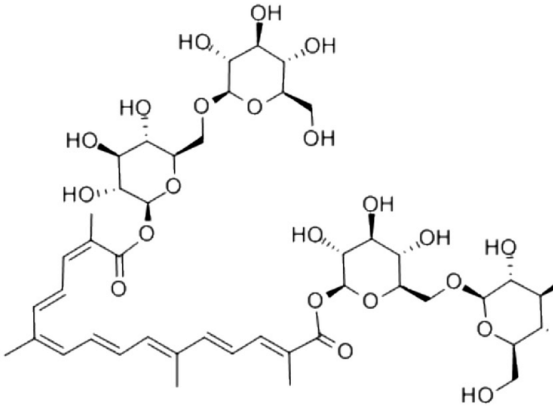
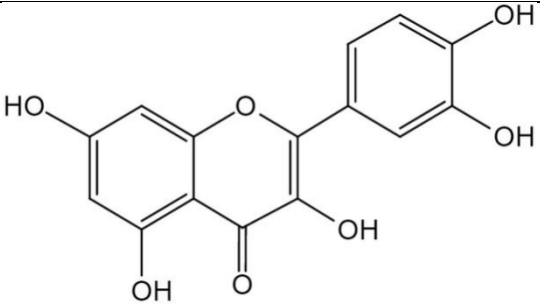
Table 1: Nephroprotective drugs and their chemical constituents along with structures

Drug source& family	Active constituent	Specific constituents	Structure
Artemisia annua (Asteraceae)	Artemisia ketone	Artemisiaketone, αpinene &1,8-cineole	 Artemisia ketone
Curcuma xanthorrhiza (Zingiberaceae)	Xanthorrhizol	Xanthorrhizol	 Xanthorrhizol
Zingiber officinale (Zingiberaceae)	Catechols	Gingerols Polyphenols	 Gingerols
Aervalanata Amaranthaceae	Flavonol glycoside	Kaempferol Rhamnoside kaempferol- 3-rhamnogalactoside	 Kaempferol
Curcuma longa (Zingiberaceae)	Terpenoid	Curcumin, curcuminoids	 Curcumin

Andrographis paniculata (Acanthaceae)	Diterpenoid	Andrographidoids	 Andrographidoids
Berberis vulgaris (Berberidaceae)	Alkaloids	Berberine	 Berberine
Camellia sinensis(Theaceae)	Flavonoids	Epicatechin, epicatechingallate, epigallocatechin	 Epicatechin
Ceratonia siliqua(Leguminosae)	Polyphenol	Carob polyphenols	 Carob polyphenols

Nigella sativa(Ranunculaceae)	Benzoquinones	Thymoquinone	 Thymoquinone
Panax ginseng(Araliaceae)	Steroid glycosides, triterpenesaponins	Ginsenosides Rh4 & Rh3	 *Ginsenosides*
Cordyceps cicadae(Clavicipitacea)	Sterol	Ergosterol	 Ergosterol
Picrorhizakurroa(Scrophulariaceae)	Glycosides	Picroside I and Kutkoside	 Picroside I

Polyporusumbellatus(Polyporaceae)	Alkaloids	Ergone, ergosterol	 ergone ergosterol
Ramulusmori(Moraceae)	Flavonoids, flavonol, Diglucoside	Rutin, quercetin, morin, mulberroside A.	 Quercetin  Rutin
Solanum xanthocarpum(Solanaceae)	Glycoalkaloid	Solasodine	 Solasodine

Polyporusumbellatus(Polyporaceae)	Alkaloids	Ergone	 Ergon
Saturejakhuzestanica(Lamiaceae)	Monoterpenoid	Carvacrol	 Carvacrol
Crocus sativus L. (Iridaceae)	Carotenoid	Crocin	 Crocin
Phoenix dactylifera L. (Arecaceae)	Flavonoids	Quercetin	 Quercetin

3. CONCLUSIONS

There are varieties of nephrotoxic agents which include different classes of drugs, heavy metals, solvents, pesticides, and NSAIDs which cause cell necrosis and lead to renal injury associated with kidney damage. The presented review has been described different kinds of nephrotoxic agents which induce kidney damage and nephroprotective plants which are essential phytochemical constituents used in the treatment of kidney damage. All plants which are studied had nephroprotective activity. Many herbs are effective as nephroprotective agents, and many more are claimed to be so, however, there is no scientific proof to back up such claims. The details of the efficacy and safety studies for these plants need to be investigated

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