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REVIEW ARTICLE

Role of seaweeds in drug induced nephrotoxicity

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ABSTRACT

Kidney is an important organ which is necessary for the body to perform various important functions which include blood purification, expelling metabolic wastes and managing water and electrolytes balance in the body. In this era of modern science, many synthetic drugs are used on patients to examine their therapeutic properties. Unfortunately, some drugs cause negative effects resulting in renal damage. Drug induced nephrotoxicity results in serious clinical syndromes, such as chronic kidney disease (CKD) and acute kidney injury (AKI). Synthetic drugs not only cure diseases but also cause some side effects in the human body. Instead of looking for synthetic drugs to cure diseases, it is necessary to consider natural drugs that maximize side effects of synthetic drugs and reduce therapeutic consequences with the most effective and dynamic healing effects. Research and utilization of marine algae have increased markedly from the last several decades. Seaweeds have also been used as drugs or drug sources over a large number of years going back into folk medicine. Since consumption of seaweeds as human food or animal feeds is increasing rapidly. In the current review, we have summarized the information regarding the drugs which cause nephrotoxicity and marine algae as seaweeds used for the treatment of nephrotoxicity.

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Introduction

The presence of any kidney injury caused by medication directly or indirectly is called drug induced nephrotoxicity. Symptoms vary from acute or chronic in which decreased Glomerular Filtration Rate (GFR) to nephrotic syndrome and Hydro Electrolytic Disorders (HED) associated with tubular damage and glomerular filtration (Kane-Gill & Goldstein, 2015). Other serious clinical syndromes include AKI and CKD which ultimately lead to End Stage Renal Disease (ESRD) (Awdishu & Mehta, 2017). According to epidemiological studies showed that nephrotoxicity to be the third most common cause of acute kidney disease, which is going to be worse in recent decades due to the more frequently use of drugs

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that can cause kidney damage (Sales & Foresto, 2020; Sohail et al., 2021). It is estimated that 20% of nephrotoxicity is raised by drugs and 66% increased by the extent of drug usage (Kim & Moon, 2012; Yousaf et al., 2022). Numerous renal toxicities include acute and chronic interstitial nephritis, proximal renal tubular acidosis (Patel & Sapra, 2020).

Metabolic Functions of Kidney

Kidney is an important organ in our body which performs several important functions like blood purification, expelling metabolic wastes and managing water and electrolytes balance in the body (Ekinci Akdemir et al., 2017). Kidney dysfunction causes decline in the kidney by many aspects like an infectious disease, abnormal functioning of the immune system, high sugar level, malignant growth etc. (Chielle et al., 2015; Nisha et al., 2017). Besides their excretory role, their role in drug and chemical biotransformation is also crucial because drug elimination and detoxification both are main functions of the kidney which makes it an important organ (Garza et al., 2022). The transport mechanisms in the kidney are well known by electrolyte and acid-base disorders are also interrupted by drugs. If a person is already suffering from kidney diseases, then their medication should be carefully examined in order to prevent them from further nephrotoxic agents. Hence, precaution for kidney harm should be at forefront for methodologies to fight against drug-induced nephrotoxicity (Patel & Sapra, 2020). Despite nephrotoxicity, hepatotoxicity is also caused by a number of drugs i.e.; acetaminophen (AAP), methotrexate (Yan et al., 2018; Sajith et al., 2020) that ultimately cause liver damage (Rane et al., 2016). Liver also significantly contributes in biotransformation of drugs and toxins for the fulfillment of many functions such as carbohydrate, fat and protein metabolisms. Liver is also the main site of drug-induced damage. From ages, an upward trend has been witnessed in kidney and liver diseases worldwide (Ekinci Akdemir et al., 2017). Nephrotoxicity and hepatotoxicity are the two major concerns to the pharmaceutical companies and also to the Food and Drug Administration (FDA) (Beger et al., 2010; Zhang et al., 2012).

Role of Drugs in Nephrotoxicity

Researchers reported in literature that a lot of synthetic drugs with wide range of antibiotics or chemicals which causes nephrotoxicity and hepatic failure (Figure 1) (Perazella, 2018) including, cisplatin, acetaminophen (AAP), and, carbon tetrachloride (CCl_4) (Zamzami et al., 2019; Sohail et al., 2019, 2021). The most significant class of antibiotics executing toxic effects on kidney function is aminoglycosides which include gentamicin. Nephrotoxicity occurs in 10% to 25% of the cases who take gentamicin for 3 to 5 days (Saleh et al., 2016). Moreover, it decreases antioxidant enzyme activity and raises the reactive oxygen species (ROS) production (Erjaee et al., 2015). Vancomycin is an antimicrobial drug which causes nephrotoxicity in 10% to 20% of patients. Similarly, Cisplatin, (cis-diammine-dichloroplatinum (II), CDDP) is also the most significant nephrotoxic drug which is filtered at the glomerulus freely and absorbed into tubular cells of the kidney via transport-mediated process (Ciarimboli, 2014). It is normally used for the treatment of solid tumors that causes acute kidney damage after assemblage in the renal tubules (Sherif, 2015). For more than 25 years, it has been recognized that cisplatin causes nephrotoxicity and may cause various diseases including AKI, inadequate reabsorption in the proximal renal tubules, chronic kidney damage, deficiency of magnesium and calcium (Miller et al., 2010; Sohail et al., 2021). Although, from both clinical observations and animal experiments there is evidence which indicates that AKI is an independent risk for CKD as well (Shi et al., 2018). Commonly, the beginning of renal inadequacy starts after a few days of cisplatin dosage, evident by increased kidney profile (urea, creatinine & BUN). Another common occurrence is hypomagnesaemia, especially after dosage of cisplatin; nephrotoxicity has been identified even in the complete absence and reduction in glomerular filtration rate which is a high risk factor for cisplatin (Miller et al., 2010). As the dose of cisplatin increases the rate of nephrotoxicity also increases (Glezerman & Jaimes, 2016). Likewise, doxorubicin is another anti-cancer nephrotoxic drug which imbalances the functions between free radicals and antioxidants and therefore causes injuries in renal tissue (Ayla et al., 2011). Even though, usage of non-steroidal anti-inflammatory drugs (NSAIDs) i.e., AAP is linked with adverse renal effects which are approximately 1 to 5% among all patients (Solomon et al., 2017). The pharmacological effects of NSAIDs are dose and duration dependent, which predisposes the involvement of specific organs, and after liver the second one most affected is the kidney (Lucas et al., 2019). AAP is usually available as an over the counter drug and is widely available over the counter (OTC) in the UK and Australia (Lau et al., 2016). It is useful in mild to moderate pain of headache, myalgia and postpartum pain (Fokunang et al., 2018). It causes acute renal failure in 1–2% of patients (Canayakin et al., 2016; Hiragi et al., 2018). It is one of the most commonly consumed medications and its toxicity causes acute liver failure (ALF) which is reported in the United States (Rubin et al., 2018). NAPQI (N-Acetyl-p-benzoquinone) is present in the microsomal P450 enzyme system, which oxidize the major part of AAP taking away by

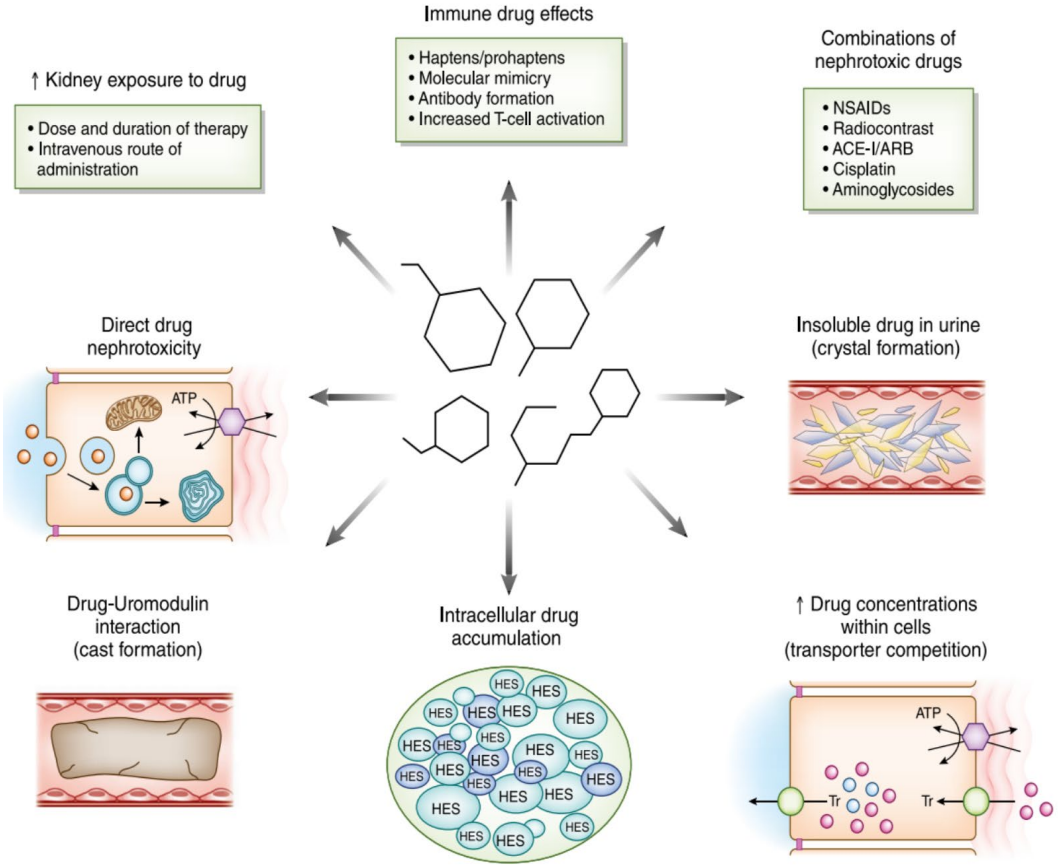

Figure 1. A prescribed mechanism of drug factors associated with increased risk for nephrotoxicity (Perazella, 2018).

GSH (intracellular glutathione) in therapeutic doses (Athersuch et al., 2018). The main symptom of acute kidney injury is acute necrosis in renal tubules caused by AAP toxicity by examining the level of kidney parameters (urea & creatinine) (Mazhar & Akram, 2016). When the drug toxicity is elevated in any organism, the free radicals are produced and oxidative stress performs a significant act in AAP which causes progressive kidney failure and also severe liver damage (Kheradpezhouh et al., 2010; Wang, 2017). Although these effects, warnings, and associations have been documented, acetaminophen remains a safe and effective medication when used correctly. The current manufacturer dose recommendation is limited to between 3 and 3.25 grams in 24 hours, depending on the formulation. However, toxicity is rare at less than 150 mg/kg for an adult or 200 mg/kg for a child (Gerriets et al., 2018).

Biomarkers of Drug Induced Nephrotoxicity

Biomarkers of kidney toxicity

Creatinine, urea and blood urea nitrogen (BUN) are the basic kidney parameters for the detection of nephrotoxicity in clinical laboratories. Healthy kidneys filter creatinine and other waste items which leave from our body in the form of urine. Therefore, determination on level of serum creatinine is necessary whether acute or chronic kidney diseases evaluation (Ostermann & Joannidis, 2016). BUN occurs in the liver as an end product and 15% excreted in the gastrointestinal (GI) tract and remaining through the kidney. The raising in BUN can also show kidney injury (Zachariah et al., 2019).

Beside these parameters, electrolytes also perform main functions in the kidney. The balance of electrolytes and fluidity is controlled by the kidney but if there is any dysfunction it causes acute or chronic kidney failure. Electrolytes include magnesium (Mg), phosphorus (P), potassium (K), sodium (Na) and calcium (Ca) which can be affected and lead to a range of side effects (Dhondup & Qian, 2017). Patients with CKD and ESRD experience both hyperkalemia and hypokalemia (Clase et al., 2020). The Na concentration is important for maintaining balance between acid-base and fluid and for neuromuscular function. The imbalance of Na level particularly those who have CKD, because kidneys have the ability to manage dilution and concentration level that gets damaged and finally causes kidney disease (Lim et al., 2016). Hyponatremia could also be a consequence of diuretic usage in these patients (Wolfe et al., 2010). Mg concentrations are also maintained by the kidney. The magnesium levels deteriorate when renal function does not perform properly (Cunningham et al., 2012). However, those patients who have CKD and ESRD have normally low magnesium levels (hypomagnesaemia) (Alhosaini et al., 2014).

Furthermore, Ca and P have reciprocal connection between each other and get imbalance during kidney injury. The symptoms associated with hypocalcemia include; Muscle cramp, disturbance in the brain, removal of mineral salts from bones, congestive heart failure etc. (Garrard & Jones, 2018).

On the other hand, it is not only possible that nephrotoxic drugs have a toxic effect on the kidney only but it also ultimately causes hepatotoxicity including hepatocellular damage, cholestasis and even tumor production (Patel et al., 2016). List of blood markers for estimating hepatotoxicity is given below:

Biomarkers of liver toxicity

Liver markers include enzymes in which Lactate dehydrogenase (LDH), Aspartate aminotransferase (AST), Alanine aminotransferase (ALAT), Alkaline phosphatase (ALP) and bilirubin (Total bilirubin & direct bilirubin). ALAT is found in various organs like kidneys, liver, heart, and muscles. It occurs in cytoplasmic form and breaks the transamination reaction. Any sort of hepatic damage can increase the level of ALAT (Aulbach & Amuzie, 2017). It may be because of hepatitis, ischemic hepatic damage that causes liver damage. AST function is to replace the amino groups from glutamate to oxaloacetate to form aspartate which is used in the urea cycle as a by-product of nitrogen. Aspartate is utilized in the urea cycle and it's rising in patients with cirrhosis and even in hepatic injury that usually raise ALAT (Fikry & Ahmed, 2019). ALP is an enzyme which is found in renal tubules, liver etc. The main function of ALP is transport of the lipid in small intestines and bones calcification. Bones around 50% activate the ALP. The raise level of ALP usually occurs by acute viral hepatitis and others include; hepatic injury etc. Conversely, if ALP level is low then it causes hypothyroidism, zinc (Zn) deficiency, hypophosphatasia etc. (Fikry & Ahmed, 2019). LDH is an enzyme which performs a function to break the conversion of lactate to pyruvate. This enzyme is present in a vast variety of cells in the body. LDH content is present in various organs like; heart, kidney, liver, and muscle. Its production has been shown to be increased under hypoxic conditions in different cell lines (Yada et al., 2016).

Bilirubin is present in every person's blood and feces in the form of yellow pigment which proceeds by the liver. The liver can't process the bilirubin in case of an excess amount of bilirubin or inflammation in the liver. It is also reported that disturbance in bilirubin might increase the chances of certain heart diseases (Kwak et al., 2012; Fujiwara et al., 2018).

Beside these markers, lipid profile (Triglyceride & total cholesterol) and glucose are also key biochemical markers of nephrotoxicity and hepatotoxicity (Gill, 2016). The metabolism of lipids is actually the catabolic and anabolic of lipids in cells either to break down or store the fats. These fats are relatively consumed from food or they are synthesized in animal's liver for energy purposes. In the human body, excess amounts of lipid are present in the form of triglycerides and total cholesterol (Baynes, 2014). Furthermore, the system of kidney filtration can be damaged by raised levels of glucose because it goes into the bloodstream that may cause the kidneys to filter an excessive amount of blood (Triplitt, 2012).

Antioxidants markers

Antioxidants can mediate at first in the pathogenesis of renal damage by completely removing ROS. The research study in cells and tubules of nephrons and AKI in animal models have recognized nephron-defensive agents with antioxidant activities that decrease oxidative harm in the kidney (Panizo et al., 2015; Ratliff et al., 2016). In animal models the research clearly showed the increased level of oxidative stress and reduced tissue antioxidant status after nephrotoxicity (Dennis & Witting, 2017). Moreover, oxidative stress and ROS are considered to be driving factors in other chronic diseases that introduce the AKI include heart disease and diabetes (Ratliff et al., 2016).

Inflammatory cytokine in drug induced nephrotoxicity

Inflammation is the body's immune response which performs a significant function in progression of AKI (Black et al., 2019). Cytokines are nonstructural proteins which include interferon, chemokines, interleukins and tumor necrosis factors (Ferreira et al., 2018) which are transported in the form of paracrine and autocrine pathways. They are involved in different forms of diseases and disturbance in the immune system by anti and pro-inflammatory systems (Spangler et al., 2015). The pro-inflammatory effects in cytokines include TNF-α (tumor necrosis factor), IL-17 (interleukin-17), IFN-y (interferon) and anti- inflammatory cytokines effect includes IL-4, IL-1ra and IL-10 and (Su et al., 2012). The inhibition in cytokines is linked with recovery of cisplatin which causes nephrotoxicity (Perse & Veceric-Haler, 2018). In this manner, new molecules are searched out that regulate kidney injury which is an important research zone that may lead to therapies to inhibit cisplatin-induced kidney injury (Humanes et al., 2017). Pro and anti-inflammatory cytokine relations work alone and sometimes merge with different types of cytokines responsible for up or down regulation of the rest of cytokines and some cytokines may have both inflammatory effects. It is typical for various cell types to emit a similar cytokine or for a single cytokine to follow up on a few diverse cell types (Pleiotropy) (Monastero & Pentyala, 2017).

Role of Medicinal Plant in Nephrotoxicity

God created everything on this earth which has a positive effect in contrast to humans who made things/medicines. To consider the side effect of drugs causes nephrotoxicity so researchers are looking for alternatives particularly coming from natural sources. There are some medicinal plants which are utilized to reduce the multiple illnesses for a very long time while they are being acceptable, reasonable, safe and accessible (Kasole et al., 2019). Natural or herbal therapeutics field has become one of the most famous trends because herbal products not only contain multicomponent therapeutics rather it also achieved a significant role in the health system for both humans and animals throughout the world (Pathak & Das, 2013). Numbers of evidence have reported that supplements from herbal medicine have potential to become a valuable complementary therapy in the treatment of various renal diseases (Roozbeh et al., 2013; Vahekeni et al., 2019).

Chinese herbal medicine (CHM) is a Traditional Chinese medicine (TCM), which has begun to attract academic attention in the world of western medicine. In past years, CHM aimed to develop new drugs for different varieties of diseases which affect human beings (Gu & Pei, 2017). China and other countries usually use CHM and it is ready to use in both the traditional and modern world (Pan et al., 2011). TCM theory is generally utilized in Asia and progressively worldwide to avoid CKD. The theoretical system of CHM is clearly different from conventional medicine and based on the differentiation of syndromes and patterns. The prescriptions are structured independently according to the patient's constitution and disease progression (Huang et al., 2018).

Medicines have many side effects which are used for the treatment of kidney damage, so herbal medicine performed a pivotal role in the prevention of many kidney diseases which are given in Table 1.

Role of Seaweeds in Drug Induced Nephrotoxicity

Over the last decade, researchers have developed an interest to focus on the significant role of algae which is a main source of a wide range of metabolites. Marine algae utilization and research have increased significantly in recent decades (Milledge et al., 2019). Marine algae have begun to gain attention as rich sources of various bioactive compounds with biomedical potential and great pharmaceuticals. It produces various compounds with great pharmacological activities such as anti-inflammatory, anticancer, antifungal, antimicrobial, antiviral etc. (Wali et al., 2019). Marine organisms survive in complex communities and live in close association with other organisms in competitive and hostile environments (Martins et al., 2014). They produce complex secondary metabolites as a response to ecological pressures such as predation and tide variations, competition for space. They serve as a source of natural products with therapeutic and nutritional properties. Moreover, the biomedical efficacy of several bioactive compounds derived from marine organisms has been experimentally demonstrated. Nowadays, researchers have demonstrated the various therapeutic properties of marine algae, which are verified *in-vivo* as well as *in-vitro* (Martins et al., 2014; Kim et al., 2018).

In Asian countries, seaweeds (marine algae) have been used as food for a long time. The estimated range of seaweeds is probably around 45,000 species. Researchers have been studying seaweed which is used as an alternative source for decades and found that it is one of the important resources for new therapeutics (Nedumaran & Arulbalachandran, 2015; Babu & Rengasamy, 2017). Seaweeds are also receiving attention for their bioactive metabolites like alkaloids, glycosides, flavonoids, saponins, tannins and steroids (Khalid et al., 2018). They may possess antiviral (Gheda et al., 2016), antibacterial (Shannon & Abu-Ghannam, 2016), antifungal (Mickymaray & Alturaiki, 2018), anticancer (Gutiérrez-Rodríguez et al., 2018; Sohail et al., 2021), antioxidant (Tariq et al., 2015), hypoglycemic (Akhtar et al., 2019), hypocholesterolemic (Ruqqia et al., 2015), hepato and renoprotective (Sohail et al., 2019, 2021) activities.

Phaeophyceae (Brown seaweed)

Brown seaweeds have the potential to provide an alternate source for solving many biomedical problems, including oxidative damage (Gomez-Zavaglia et al., 2019). *Sargassum*, a genus of brown seaweed, commonly known as sea holly or gulf-weed belongs to the family *Sargassaceae* and contains approximately 400 species (Kanimozhi et al., 2015). Fucoxanthin is the main pigment in brown seaweeds, which is one of the most abundant carotenoids in nature (10% of estimated total carotenoid production) (Pangestuti & Kim, 2011). However, different strains of brown seaweed have different profiles and compositions of fucoxanthin. Previous studies reported that fucoxanthin has anti-cancer, anti-diabetic, anti-oxidation, anti-carcinogenic, anti-inflammatory, anti-obesity and hepato-protective activities as well as cerebrovascular and cardiovascular protective effects (D'Orazio et al., 2012; Zhang et al., 2015).

Table 1. Effective role of medicinal plants used for the treatment of nephrotoxicity

S.No.	Plant	Part of Plant	Animal	Outcome	References
1	*Enicostemma littorale*	Whole plant	Rat	• Improvement in blood biochemical parameters • Increase antioxidant parameters • Amelioration in kidney histology	Bhatt et al. (2011)
2	*Ficus hispida*	Whole plant	Rat	• Amelioration in urine and blood biochemical parameters • Improvement in kidney histology and oxidative stress in both prophylactic and curative groups	Swathi et al. (2011)
3	*Nigella sativa*	Seeds and oil	Rat	• Normalization of the renal function • Improvement in oxidative stress • Amelioration of apoptotic markers • Amelioration in kidney histology	Salama et al. (2011)
4	*Cassia occidentalis*	Leaves	Rat	• Improvement in urine and blood biochemical parameters • Improvement in oxidative stress • Amelioration in kidney histology	Gowrisri et al. (2012)
5	*Phaseolus radiates*	Seeds	Rat	• Amelioration in blood biochemical parameters	Chaware (2012)
6	*Punica granatum*	Fruits	Rat	• Amelioration in kidney histology and blood biochemical parameters which were better when the extract co-administered with gentamicin which-induced nephrotoxicity	Ali & Saeed (2012)
7	*Khaya senegalensis*	Stem bark	Rat	• Amelioration in blood biochemical parameters • Betterment in hematological parameters • Amelioration in kidney histology	El Badwi et al. (2012)
8	*Ginkgo biloba*	Leaves	Rat	• Amelioration in blood biochemical parameters • Improvement in oxidative stress • Amelioration in kidney histology	Okuyan et al. (2012)
9	*Heliotropium Eichwaldi*	Root	Mouse	• Amelioration in blood biochemical parameters • Improvement in oxidative stress • Amelioration in kidney histology	Sharma & Goyal (2012)
10	*Moringa oleifera*	Leaves	Rat	• Amelioration in blood biochemical parameters • Decreased in kidney lipid peroxidation • Amelioration in kidney histology	Ouédraogo et al. (2013)
11	*Tephrosia purpurea*	Leaves	Rat	• Amelioration in blood biochemical parameters • Improvement in oxidative stress and histology of kidney in both curative and preventive groups	Jain et al. (2013)
12	*Nigella sativa*	Thymoquinone	Rat	• Amelioration in blood biochemical parameters • Improvement in oxidative stress • Amelioration in kidney histology	Kensara (2013)
13	*Vaccinium myrtillus*	Whole plant	Rat	• Improvement in oxidative stress • Amelioration in kidney histology	Pandir & Kara (2013)
14	*Curcuma longa*	Curcumin	Mouse	• Amelioration of kidney function • Decrease in intercellular adhesion molecule-, renal tumor necrosis factor-α and monocyte chemoattractant protein-1 • Improvement of kidney histology	Ueki et al. (2013)
15	*Curcuma longa*	Curcumin	Rat	• Amelioration in blood biochemical parameters • Improvement in oxidative stress • Amelioration in kidney histology	Palipoch et al. (2013)
16	*Cissampelos pareira*	Whole plant	Rat	• Amelioration in urine and blood biochemical parameters • Improvement in oxidative stress	Sekhara Reddy et al. (2014)
17	*Costus afer*	Leaves	Rat	• Amelioration in blood biochemical parameters • Amelioration in kidney histology	Ezejiofor et al. (2014)
18	*Elaeocarpus ganitrus*	Seeds	Rat	• Amelioration in urine and blood biochemical parameters • Improvement in oxidative stress • Amelioration in kidney histology	Kakalij et al. (2014)
19	*Myristica fragran*	Fruits	Rat	• Amelioration in blood biochemical parameters • Improvement in oxidative stress	Nivetha & Prasanna (2014)

Table 1 (continued)

S.No.	Plant	Part of Plant	Animal	Outcome	References
20	*Pistacia khinjuk*	Fruits	Rat	• Amelioration in blood biochemical parameters • Improvement in oxidative stress	Ghaedi et al. (2014)
21	*Tamarindus indica*	Fruits	Rat	• Amelioration in urine and blood biochemical parameters • Amelioration in kidney histology	Ullah et al. (2014)
22	*Punica granatum*	Flowers	Rat	• Amelioration in blood biochemical parameters • Improvement in oxidative stress • Amelioration in kidney histology	Motamedi et al. (2014)
23	*Turmeric plant*	Curcumin	Rat	• Increase anti-inflammatory cytokine levels • Decrease antioxidant expression	Soliman & Ismail (2014)
24	*Citrus medica*	Fruits	Rat	• Amelioration in blood biochemical parameters • Improvement in oxidative stress • Amelioration in kidney histology	Al-Yahya et al. (2015)
25	*Silybum marianum*	Silymarin	Human	• Reduction in kidney marker: creatinine, and urea 2 weeks after cisplatin administration	Momeni et al. (2015)
26	*Silybum marianum*	Silymarin	Human	• Oral administration of silymarin could not prevent cisplatin associated tubular dysfunction and nephrotoxicity in clinical study.	Shahbazi et al. (2015)
27	*Viscum articulatum*	Oleanolic acid	Rat	• Amelioration in urine and kidney biochemical parameters • Amelioration in kidney histology	Bachhav et al. (2012)
28	*Nigella sativa*	Seeds	Rat	• Amelioration in urine and blood biochemical parameters	Hosseinian et al. (2016)
29	*Plantago major*	Whole plant	Rat	• Reduction in kidney marker: creatinine, urea and in electrolytes: potassium in all extract treated animals • Raising in sodium in the extract 600 mg/kg group • Increase of superoxide dismutase and reduction in malondialdehyde concentration activity in extract 1200 mg/ kg group • Increase of catalase activity in all extract-treated animals	Parhizgar et al. (2016)
30	*Nigella sativa and Curcuma longa*	Nigella sativa: Seeds Curcuma longa: rhizome	Rat	• Improvement in oxidative stress	Mohebbati et al. (2017)
31	*Matricaria chamomilla*	Whole plant	Rat	• Normalization of the renal parameters • Improvement in oxidative stress • Amelioration of apoptotic markers • Amelioration in kidney histology	Farouk et al. (2017)
32	*Lemongrass*	Citral	Rat	• Amelioration antioxidant activity	Uchida et al. (2017)
33	*Caesalpinia bonduc*	Whole plant	Rat	• Improvement in blood biochemical parameters • Amelioration in kidney histology	Talukdar et al. (2018)
34	*Ficus carica*	Leaves	Rat	• Improvement in blood biochemical parameters • Improvement in oxidative stress markers	El-Sayed et al. (2019)
35	*Crocus sativus*	Saffron	Rat	• Amelioration in blood biochemical parameters • Improvement in oxidative stress • Amelioration in kidney histology	Zarei & Elyasi (2022)
36	*Mangifera indica*	Whole plant	Rat	• Amelioration in blood biochemical parameters • Improvement in kidney tissue damage	Akter et al. (2022)
37	*Nigella sativa*	Oil	Rat	• Improvement in kidney parameters • Increase in catalase and superoxide dismutase activities • Amelioration in kidney histology	Jaswal et al. (2022)

Table 2. Protective role of seaweeds for the treatment of nephrotoxicity in rats

S.No	Seaweeds	Class	Outcomes	References
1	*Colpomenia sinuosa*	Brown algae	Nephroprotective effects against carbon tetrachloride (CCl_4)	Ramarajan et al. (2012)
2	*Sargassum polycystum*	Brown algae	Nephroprotective and hepatoprotective activity against diabetic effect	Motshakeri et al. (2014)
3	*Ulva lactuca*	Green algae	Nephroprotective and antioxidant activity against D-Galactose	Yang et al. (2021)
4	*Turbinaria ornate, Padina pavonia*	Brown algae	Renoprotective activity against azoxymethane	Mahmoud et al. (2014)
5	*Ulva fasciata*	Green algae	Nephroprotective activity against anti-cancer drug, cisplatin and anti-bacterial drug, gentamicin	Rizk et al. (2016) Abd El Raouf et al. (2017) Sohail et al. (2021).
7	*Porphyra yezoensis*	Brown alga	Nephroprotective activity against cisplatin	Kim et al. (2018)
8	*Stokeyia indica*	Brown alga	Renoprotective and hepatoprotective activity against acetaminophen (AAP)	Taj et al. (2019)
9	*Spirulina platensis*	Green algae	Nephroprotective activity against cisplatin	Zakaria et al. (2019)
10	*Sargassum swartzii*	Brown alga	Nephroprotective and Hepatoprotective activity against acetaminophen (AAP) and CCl_4	Hira et al. (2019)
12	*Halymenia porphyroides, Sargassum ilicifolium*	Red algae Brown algae	Renoprotective and hepatoprotective activity against acetaminophen (AAP)	Sohail et al. (2019)
13	*Sargassum angustifolium*	Brown algae	Renoprotective effect against gentamicin induced nephrotoxicity	Pourkhalili et al. (2021)
11	Chondrus canaliculatus	Red algae	Antioxidant, nephro and hemato-protective against maneb	Jaballi et al. (2019)
14	*Sargassum cinereum*	Brown algae	Renoprotective and hepatoprotective activity against Cyclophosphamide	Khalil et al. (2020)
15	*Sargassum fusiforme*	Brown algae	Reno and hepatoprotection against cisplatin	Natarajan et al. (2022)
16	*Laminaria japonica*	Brown algae	Renoprotective effect against glycerol-induced acute kidney injury	Li et al. (2017)

Rhodophyta (Red seaweed)

The Rhodophyta (red algae) are a distinct eukaryotic lineage. The red color of these algae is due to the pigments; phycoerythrin and phycocyanin. It characterizes other pigments, chlorophyll *a* (without chlorophyll *b*), beta-carotene, and other unique xanthophylls (Barkia et al., 2019). Abundantly cultivated edible red seaweed, *Eucheuma cottonii*, contains large amounts of polyunsaturated fatty acids, minerals, polyphenols, dietary fiber, vitamins, proteins, antioxidants and phytochemicals and has medicinal properties (Kania et al., 2013). *E. cottonii* showed the highest *in-vivo* antioxidant and anti-hyperlipidemic activities, elevated erythrocyte GSH-Px, and reduced plasma lipid peroxidation of high-fat diet rats toward the values of normal rats. *Gracilaria birdiae* (GB) is grown in northeast Brazil and used for food. However, little research has been done on the economic potential of this alga. Over 300 species of *Gracilaria* have been identified, of which 160 are taxonomically recognized (Sakthivel & Devi, 2015). *G. birdiae* protects both the kidney and liver of rats from CCl_4 which cause nephrotoxicity and hepatotoxicity possibly due to their antioxidant capacity (Barros-Gomes et al., 2018).

Chlorophyta (Green seaweed)

Ulva is a green alga, commonly known as sea lettuce, is widely distributed beyond coastal regions of the world and is widely used in the biotechnology, food and pharmaceutical

industries (Torres et al., 2019). Green seaweeds contain high amounts of polyphenols such as epigallocatechin gallate, epicatechin, catechin, and gallic acid (Vinayak et al., 2011). Some beneficial green edible seaweed is; *Ulva reticulata, Ulva lactuca,* etc. Ethyl acetate extract of *U. lactuca* showed the highest antifungal activity than that of other extracts against filamentous fungi and yeast. *Ulva reticulata* is widely distributed in the Indo-west Pacific region, Southwest Asia, Northern Pacific Ocean, Southeast Asia and Western and Eastern Indian Ocean. In southern India, *U. reticulata* is highly concentrated along the coastline of Tamil Nadu, especially Mannar Bay, Rameshwaram to Kanyakumari (Lalitha & Dhandapani, 2018).

Pharmacological studies indicate that fucoidan is a sulfated polysaccharide extracted from brown seaweeds that inhibits renal fibrosis and glomerular sclerosis by reducing the accumulation of extracellular matrices. It also maintains the glomerular basement membrane and glomerular structural integrity, improves glomerular filtration function, and protects renal glycosaminoglycans from abnormal degradation (Wang et al., 2019). Josephine et al. (2006, 2007) reported that isolated sulphated polysaccharide reduced blood urea nitrogen and serum creatinine level and attenuated renal tubular damage in renal glomerular injury in rats. Polysaccharides from green seaweeds, C*aulerpa racemose* (sea grapes) have been reported to be the kidney protective effects in diabetic models (Cao et al., 2021). The chemical constituents like fatty acids, alkaloids, phenolic compounds, terpernoids, were identified by GC-MS from green seaweeds like *Ulva fasciata* has nephroprotective activity (Abd El Raouf et al., 2017). The protective roles of seaweeds in nephrotoxicity are given in Table 2.

Conclusion

Worldwide kidney diseases have become a major cause for disability and even leading to death in the worst circumstances. Drugs which are usually used to treat diseases but its overdosing causes side effects and complications in the kidney and liver so there is a vast interest to search for alternative medicine which especially comes from natural sources without any side effects. The World Health Organization (WHO) reported that 80% of people rely on natural sources for some part of their primary health management needs. The main sources of these successful compounds are plants and microbes from the marine and terrestrial environments. Thereby, researchers are working on marine based natural products particularly edible seaweeds such as sea lettuce showed a promising role in attenuation of drug induced nephrotoxicity. In-addition they might be considered as potential candidates for natural based drug therapy as they minimize adverse effects of drugs particularly cisplatin and AAP. Further works are currently underway on seaweeds and other plants to discover effective medicines with fewer consequences.

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Compliance With Ethical Standards

Authors' Contributions

NS: Designed the study, Wrote the first draft of the manuscript.
HF: Support and help to complete my work with efficient manner.
Both authors read and approved the final manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest.

Ethical Approval

For this type of study, formal consent is not required.

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