Phytochemicals and Neutraceuticals: Promissing Therapeutics for Drug-Induced Nephrotoxicity.

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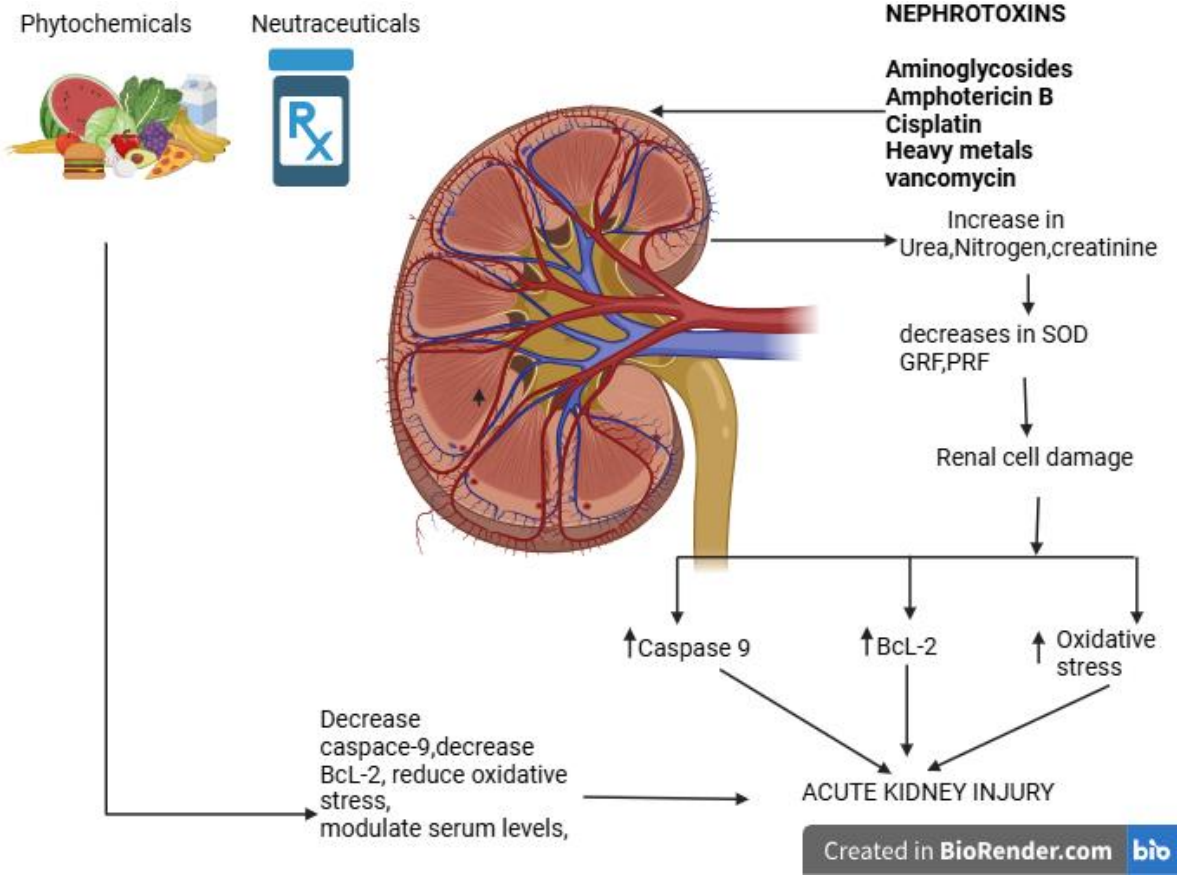
***Abstract*—An important health concern that can occur as a side effect of several drugs is drug-induced nephrotoxicity. The main symptom of this illnessis hypovolemia, which might affect kidney function by constricting the afferent arteriole. Nephrotoxicity is more common in some populations, including those with heart failure, sepsis, and chronic dehydration. This is due to drugs like NSAIDs,cyclosporines and chemotherapeutic agents like cisplatin. These medications harm people via a number of pathways, such as inflammation, mitochondrial damage, and oxidative stress (Reactive oxygen species). Nutraceuticals and phytochemicals have demonstrated promise in reducingnephrotoxicity. Green tea, curcumin and flavonoids are examples of medicinal plants having anti-inflammatory and antioxidant qualities that have shown nephroprotective effects in preclinical research.In diseases like acute kidney injuryresveratrol and naringeninfor instance have been demonstrated to decrease oxidative damage and enhance renal function. The anti-inflammatory and antioxidant properties of nutraceuticals, such as omega-3 fatty acids, have also made them promising therapeutic agents for preserving renal function. This review looks at how drugs cause nephrotoxicity, how phytochemicals and nutraceuticals protect the kidneys and how they might be used therapeutically to stop drug-induced renal damage.**

***Index Terms*—Drug-induced nephrotoxicity, Phytochemicals, Oxidative stress, Nephroprotective, Resveratrol, Flavonoids, Omega-3 fatty acids.**

I. INTRODUCTION

Medication is widely used worldwidetypically accessible without a prescription, and is thought to be one of the primary causes of drug-induced nephrotoxicity. Relative hypovolemia is the primary risk factor because it inhibits prostaglandins, which causes the afferent arteriole to constrict. Patients with sepsisdecompensated congestive heart failure, cirrhosis, dehydration, or those using medications that affect renal hemodynamics (such as cyclosporine, iodinated contrast, or RAAS inhibitors) are examples of sensitive groups.Nearlyevery renal compartment can sustain damage from NSAIDS.Drug-induced thrombotic microangiopathy is caused by direct toxicity to renal epithelial cells or inflammation that damages organs. Antiplatelet medications such as quinine, cyclosporin, and mitomycin-C causes thrombotic microangiopathy [1] [2].Cisplatinis a well-known platinum compound used in the treatment of several cancers, sarcomas, and lymphomas. However, after using high-dose medications 20% of people develop serious kidney problems.The glomerulus can freely filter the unbounded cisplatin, which drug transporters can then absorb and store in renal tubular cells causing renal damage [3].ROS (reactive oxygen species) that damages mitochondria. Depending on the precise site of injury and the underlying pathophysiological pathways, drug-induced nephrotoxicity can take many different forms and the most common nephropathies caused by drugs[4].Drugssuch asangiotensin-converting enzyme blockers [ARBs], NSAIDs, cyclosporine, and tacrolimus can cause nephrotoxicity by changing intraglomerular hemodynamics and lowering GFR.Acyclovir, ganciclovir, ampicillin, ciprofloxacin, sulfonamides, methotrexate, and triam-terene are among the medications linked to crystal nephropathy because of calcium phosphate crystal deposition and uric acid, chemotherapy can also cause crystal nephropathy [5].Renal toxicity from sulfasalazine has been documented as an idiosyncratic, dose-independent condition that manifests as a widespread hypersensitivity reaction. However, it has been noted that mesalazine causes nephritis in a considerable proportion of patients while it is being administered [6]. Increased activity of the enzymes that produce free radicals, decreased activity of the enzymes that remove them and low antioxidant levels all contribute

to oxidative stressThe mitochondria are among the most major targets of ROS's damaging effects. In order to cause cell death oxidative damage results in mitochondrial malfunction and membrane loss which sets off the mitochondrial permeability transition (MPT) and release of proapoptotic proteins such cytochrome c [7].



II. PHYTOCHEMICALS AND NEUTRACEUTICALS

Herbal medicines are so inexpensive and have few harmful side effects, demand for them is rising quickly in both industrialized and developing nations.From medicinal plants, phytochemicals with potential for efficient treatment of renal problems can be found and separated. Worldwide screening is being done on thousands of herbal and traditional substances and their sources to confirm their utility in renal diseases.Along with their mode of action the majority of scientific research have shown the advantages of medicinal plants for the treatment of KD(kidneyDisease). Furthermore, by keeping an eye on blood urea nitrogen (BUN), uric acid, and serum creatinine (Cr) levels as well as the negative effects of dialysis, medicinal plants might reduce the financial load [8]. The active ingredient in licorice, glycyrrhizin, is a hydrophilic portion of GA (Glycyrrhizic Acid) which is a conjugate of two glucuronic acid molecule. It has anti-inflammatory, anti-ulcer, anti-allergic, antioxidant, antiviral, and anti-tumor properties and is utilized as a flavoring agent in several sweets and medications [9].Green tea is said to include compounds that help prevent nephrotoxicity, including catechin, epigallocatechin, and epigallocatechin gallate (EGCG). A study on mice given cisplatin found that pre-treating the mice with polyphenols (EGCG and epigallocatechin) decreased toxic alterations, cisplatin-induced adverse effects, and enhanced kidney function. Additionally, it was shown that administering mice 20–40 mg/kg of EGCG and catechin decreased tumor necrosis factor-alpha (TNF-alpha), malondialdehyde (MDA), and raisedglutathionelevels. According to a different rat

study, EGCG has nephroprotective qualities by preventing oxidative stress, regulating systemic inflammation and leucocytosis and shielding polyphenol from the negative consequences and death caused by cisplatin-induced nephrotoxicity [10].Strong anti-inflammatory and antioxidant properties are attributed to curcumin. Furthermore, it is a potent scavenger of nitrogen dioxide, hydroxyl radicals, and the superoxide anion. It also shields DNA against strand breaks caused by singlet oxygen. Turmeric contains hepatoprotective and nephroprotective properties that enhance creatinine and urea clearance, uric acid, and prevent chronic renal allograft nephropathy caused by pharmaceutical medications like cisplatin or doxorubicin-induced nephrotoxicity. Antioxidative enzyme induction has been proposed as the explanation for these advantageous effects [11].

III. PHYTOCHEMICALS IN DRUG INDUCED NEPHROTOXICITY

C. intybus tincture decreased oxidative stress in AKI (Acute kidney injury) rats by raising TAC and decreasing TOS, OSI, and NOx in a reverse concentration-dependent mannerwith CHT 1:1 exhibiting the lowest antioxidant activity. Since the samples had no visible effect on MDA and SH the C. intybus tincture had no effect on lipid peroxidation or thiols.Byreducing the transcription factor NF-kB in a reverse concentration-dependent mannerlower doses being a more effective inhibitorC. intybus tincture also demonstrated anti-inflammatory properties.Flavonoidsand caffeic acids are found in C. intybus. Numerous research on flavonoids (such as luteolin, apigenin, quercetin, and rutin) have shown that they have nephroprotective and diuretic effects. Additionally, polyphenolic acids have been investigated for their significant involvement in restoring renal function after oxidative stress [12].

IV. POLYPHENOLS

Numerous studies have demonstrated that polyphenols can counteract a number of variables associated with AKI (acute kidney injury). A naturally occurring polyphenol that is a member of the stilbenes class is resveratrol (3,5,4′-trihydroxystilbene). It is the most researched polyphenol that has demonstrated possible protection against AKI and is found in a wide variety of plantsResveratrol decreased several markers of renal function as well as the pathological damage caused by AKI.Resveratrol reduced ROS (Reactive Oxygen Species) in HK-2 human kidney cells, demonstrating its efficacy against AKI [13].It is evident that EME (extract of M.emarginatao) lowers blood urea levels in comparison. when gentamicin was the only medication taken.*Ginkgobiloba*extract can lower high bloodurea levels because of gentamicin-induced nephrotoxicity [14].

V. FLAVANOIDS

Flavanoidsmodulates oxidative stress and downregulating TGF β1 and IL-1, naringenin, a flavonone most commonly found in grapefruit, orange, or tomato peel/skinimproved renal impairment caused by STZ in diabetic rats. Additionally, diabetic rats treated with naringenin showed better kidney histology and a marked decrease in apoptotic activity [15]. Flavonoids are categorized into various groups based on the degree of saturation and oxidation of the C-ring as well as the different connections between the B-ring and C-ring. These groups include flavones (like apigenin, rutin, and luteolin), flavonols (like quercetin, kaempferol, myricetin, and fisetin), flavanols (like epigallocathechin),isoflavonoids (like genistein and daidzein), flavanones (like naringin, naringenin, and hesperidin), and anthocyanidins (like apigenidin, cyanidin, and malvidin). Flavonoids have gained popularity in recent years.Experimental and epidemiological research have demonstrated the positive health effects of flavonoid consumption. As potent antioxidants flavonoids can shield plants from harmful environmental factors. Flavonoids have therefore been investigated for potential positive effects on a range of acute and chronic human illnesses [16].

VI. ALKALOIDS

Alkaloids can be classified into several classes or groups according to their chemical structures and characteristics. These include pyrrolizidine(senecionin&retronecin) indole (serotonin, melatonin, and tryptamine), isoquinoline

(morphine, codeine, and papaverine), andterpenic(atropine, scopolamine&ephedrine).A variety of alkaloids has pharmacological characteristics including analgesic, hallucinogenic, anesthetic, antidiabetic, and anticancer characteristics.Research indicates that plants that generate the alkaloids harmine, harmaline, and tetrahydroharmine may possess nephroprotective biological activity meaning they could shield the kidneys from harm [17].

VII. TERPENOIDS

Terpeneschemical structures exhibit antioxidant action [18]. Terpenoids, sometimes referred to as isoprenoids, make up around 60% of phytochemicals and are the most abundant class of secondary metabolites found in plants. They have a unique scent and are utilized in traditional medicines and spices for their analgesic, antipyretic, and sweat-inducing properties. Terpenoids are also utilized in conventional medicine, immunology, endocrinology/reproductive dysfunction, cardioprotection, cancer prevention and therapy, immunological, anti-inflammatory, menopausal, and neuroprotective therapies [19].

VIII. NEUTRACEUTICALS IN DRUG INDUCED NEPHROTOXICITY

A diet that includes fruits, vegetables, nuts, and some types of oil seeds is thought to help prevent chronic illnesses. This is because various active ingredients known as nutraceuticals are present. Important food ingredients known as nutraceuticals include phytosterols, polyunsaturated fatty acids, and phenolic compounds. These substances have been shown to have anti-inflammatory and antioxidant properties previously.Numerous bioactive multitarget molecules are found in nutraceuticals, which gives them a broad range of applications in both human and animal disorders. They can have pharmacological and biological benefits, including antioxidant and free radical protection and have nephroprotective property [20] [21].

IX. OMEGA-3 FATTY ACID

The Major three components of omega 3 (O-3) fatty acids (FAs), alpha-linolenic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are essential nutrients they cannot be produced by the bodybut are necessary for a healthy metabolism. They change the cell membranes physical propertieswhich affects biochemical signaling on the cell surface. They also act as ligands for a number of nuclear transcription factors which changes genes expressions. The two long-chain Omega-3 FAs, EPA and DHA have been shown to be helpful in cardiovascular disorders and may prevent cognitive decline. Further benefits of Omega-3 include a decrease in renal damage.Rheumatoid arthritis inflammatory bowel disease several skin conditions and nephropathies are only a few of the inflammation-mediated illnesses for which omega-3 fatty acids have therapeutic advantages [22][23].

X. CONCLUSION

Because drug-induced nephrotoxicity can cause irreversible kidney damage and consequences including chronic kidney disease (CKD), it continues to be a serious concern in clinical settings. This condition's pathogenesis is complex and includes oxidative stress, inflammation, and mitochondrial dysfunction, all of which can cause renal impairment and cellular damage. Recent studies on the medicinal uses of nutraceuticals and phytochemicals, however, present a promising way to lessen nephrotoxic harm. In preclinical models, phytochemicals like flavonoids, polyphenols, and curcumin have shown strong antioxidative and anti-inflammatory properties that can both restore renal function and shield renal tissues from oxidative damage. Furthermore, nutraceuticals such as omega-3 fatty acids, which modulate inflammatory pathways and reduce oxidative stress, offer a safe and natural alternative to promote kidney health.Althoughadditional clinical research is required to verify the effectiveness and safety of these natural substances, new data indicates that including phytochemicals and nutraceuticals in treatment regimens may offer a useful method of avoiding or controlling drug-induced nephrotoxicity. These therapies may improve kidney health and lessen the burden of drug-induced renal impairment,

especially when paired with traditional therapeutic techniques.

REFRENCES

[1] Sales, G. T. M., &Foresto, R. D. (2020). Drug-induced nephrotoxicity. Revista da AssociaçãoMédica Brasileira, 66, s82-s90.

[2] Kim, S. Y., & Moon, A. (2012). Drug-induced nephrotoxicity and its biomarkers. Biomolecules & therapeutics, 20(3), 268.

[3] Wu, H., & Huang, J. (2018). Drug-Induced Nephrotoxicity: Pathogenic Mechanisms, Biomarkers and Prevention Strategies. Current Drug Metabolism, 19(7), 559–567. doi:10.2174/1389200218666171108l5

[4] Mody, H., Ramakrishnan, V., Chaar, M., Lezeau, J., Rump, A., Taha, K., … Ait-Oudhia, S. (2020). A Review on Drug-Induced Nephrotoxicity: Pathophysiological Mechanisms, Drug Classes, Clinical Management, and Recent Advances in Mathematical Modeling and Simulation Approaches. Clinical Pharmacology in Drug Development. doi:10.1002/cpdd.879

[5] Shahrbaf, F. G., & Assadi, F. (2015). Drug-induced renal disorders. Journal of renal injury prevention, 4(3), 57.

[6] Oikonomou, K. A., Kapsoritakis, A. N., Stefanidis, I., & Potamianos, S. P. (2011). Drug-induced nephrotoxicity in inflammatory bowel disease. Nephron Clinical Practice, 119(2), c89-c96.

[7] Hosohata, K. (2016). Role of oxidative stress in drug-induced kidney injury. International journal of molecular sciences, 17(11), 1826.

[8] Basist, P., Parveen, B., Zahiruddin, S., Gautam, G., Parveen, R., Khan, M. A., ... & Ahmad, S. (2022). Potential nephroprotective phytochemicals: Mechanism and future prospects. Journal of ethnopharmacology, 283, 114743.

[9] Arjumand, W., & Sultana, S. (2011). Glycyrrhizic acid: a phytochemical with a protective role against cisplatin-induced genotoxicity and nephrotoxicity. Life sciences, 89(13-14), 422-429.

[10] Shukla, M. K., Ranjan, A., & Bano, R. Pure Phytochemical constituents and Herbs Have the Potential to Protect Against Drug-Induced Nephrotoxicity.

[11] Abd El-Ghany, M. A., Ramadan, A. M., &Ghozy, S. F. (2012). Nutraceutical effects of curcuma, ginger, celery, yeast and honey on side effects of gentamicin induced nephrotoxicity in rats. World Applied Sciences Journal, 16(5), 646-655.

[12] Epure, A., Pârvu, A. E., Vlase, L., Benedec, D., Hanganu, D., Gheldiu, A. M., ... & Oniga, I. (2020). Phytochemical profile, antioxidant, cardioprotective and nephroprotective activity of romanian chicory extract. Plants, 10(1), 64.

[13] Guerreiro, Í., Ferreira-Pêgo, C., Carregosa, D., Santos, C. N., Menezes, R., Fernandes, A. S., & Costa, J. G. (2022). Polyphenols and their metabolites in renal diseases: An overview. Foods, 11(7), 1060.

[14] Rameshkumar, A., Sivasudha, T., Jeyadevi, R., Sangeetha, B., Smilin Bell Aseervatham, G., & Maheshwari, M. (2013). Profiling of phenolic compounds using UPLC–Q-TOF-MS/MS and nephroprotective activity of Indian green leafy vegetable Merremiaemarginata (Burm. f.). Food Research International, 50(1), 94–101. doi: 10.1016/j.foodres.2012.09.035

[15] Vargas, F., Romecín, P., García-Guillén, A. I., Wangesteen, R., Vargas-Tendero, P., Paredes, M. D., … García-Estañ, J. (2018). Flavonoids in Kidney Health and Disease. Frontiers in Physiology, 9. doi:10.3389/fphys.2018.00394

[16] Cao, Y. L., Lin, J. H., Hammes, H. P., & Zhang, C. (2022). Flavonoids in treatment of chronic kidney disease. Molecules, 27(7), 2365.

[17] Rajesham, V. V. (2023). IN SILICO DOCKING STUDIES FOR SELECTED ALKALOID COMPOUNDS FOR NEPHROPROTECTIVE ACTIVITY.

[18] Gonzalez-Burgos, E., & Gomez-Serranillos, M. P. (2012). Terpene Compounds in Nature: A Review of Their Potential Antioxidant Activity. Current Medicinal Chemistry, 19(31), 5319–5341. doi:10.2174/092986712803833335.

[19] Kang, H. G., Lee, H. K., Cho, K. B., & Park, S. I. (2021). A review of natural products for prevention of acute kidney injury. Medicina, 57(11), 1266.

[20] Al-Okbi, S. Y., Mohamed, D. A., Hamed, T. E., Esmail, R. S., & Donya, S. M. (2014). Prevention of renal dysfunction by nutraceuticals

prepared from oil rich plant foods. Asian Pacific Journal of Tropical Biomedicine, 4(8), 618–626. doi:10.12980/apjtb.4.201414b66

[21] Longobardi, C., Ferrara, G., Andretta, E., Montagnaro, S., Damiano, S., & Ciarcia, R. (2022). Ochratoxin A and kidney oxidative stress: the role of nutraceuticals in veterinary medicine—a review. Toxins, 14(6), 398.

[22] Goksu Erol, A. Y., Avcı, G., Sevimli, A., Ulutas, E., & Ozdemir, M. (2013). The protective effects of omega 3 fatty acids and sesame oil against cyclosporine A-induced nephrotoxicity. Drug and chemical toxicology, 36(2), 241-248.

[23] Hlail, A. T., Faraj, H. R., &Abdulredha, W. S. (2020). The protective effect of Omega3 against amikacin-induced nephrotoxicity in rats. Systematic reviews in pharmacy, 11(9), 110-7.