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Calcineurin inhibitors-induced nephrotoxicity: Molecular mechanisms and mitigation strategies

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Abstract: The kidney is particularly vulnerable to drug-induced toxicity because it plays a major role in the body's detoxification processes by collecting and excreting waste products and poisons. A substantial factor in renal impairment has been attributed to nephrotoxicity caused by drugs. With an outstanding short-term prognosis, the utilization of calcineurin inhibitors (CNIs), namely cyclosporine and tacrolimus, propelled significant progress in the domain of kidney transplantation. Nevertheless, the chronic nephrotoxicity of these medications is the Achilles' heel of currently used immunosuppressive therapy strategies. It has been proven that the administration of CNIs results in reactive oxygen species (ROS) generation. It has been established that oxidative stress is a potential cause of chronic allograft nephropathy (CAN). The purpose of this review is to examine the pathogenesis of nephrotoxicity associated with CNIs in an effort to discover promising drugs with reno-protective qualities that can be administered concurrently to counteract the nephrotoxicity of CNIs.

Keywords: Calcineurin inhibitors; Nephrotoxicity; Molecular mechanisms; Oxidative stress; Inflammation; Mitigation Strategies.

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1. INTRODUCTION

The kidneys are vital for blood purification because they eliminate waste and toxic substances. They also produce erythropoietin, an erythroid growth factor, regulate blood volume and pressure, and maintain electrolyte balance and bone mineral homeostasis by activating vitamin D. As a result, kidney damage causes anemia, uremia, hypertension, born-mineral problems, and irregularities in fluid balance [1,2]. Several conditions, including oxidative stress, inflammation, ischemia/reperfusion injury, and nephrotoxic substances, can cause kidney damage or inactivity [2]. The kidney's strong blood flow, diversity of metabolizing enzymes and transporters, and the ability to collect solutes during urine production make it sensitive to xenobiotics [3].

Renal disorders are becoming acknowledged as substantial financial burdens and important worldwide health concerns [4,5]. Since the kidney concentrates and eliminates poisons and medications, drug-induced toxicity targets it. It has been observed that drug-related nephrotoxicity contributes 8-60% to hospital-related acute kidney injury (AKI) [6]. Serum creatinine (sCr) rises by 0.3 mg/dL (26.5 µmol/L) or greater during 48 hours, or by at least 1.5-fold from its initial value within 7 days following treatment, to establish AKI. Drug-induced nephrotoxicity has consistently led to AKI, or chronic kidney disease (CKD), affecting around eight to thirteen percent of the population. This condition affects either men or women across all age groups, with particular emphasis on pediatrics and geriatrics, as well as those with preexisting renal complications [6,7].

Diagnosis of CKD involves a deterioration in renal function (glomerular filtration rate (GFR) <60 mL/min per 1.73 m^2) or anomalous renal damage indicators during a minimum of three months. CKD is characterized by renal fibrosis, which may result in end-stage renal disease (ESRD), which is fatal. The evolution of renal fibrosis is mostly attributed to the activation of myofibroblasts, loss of nephrons,

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inflammation, and deposition of extracellular matrix (ECM) [8]. Nephron depletion is motivated by lipotoxicity and oxidative stress [9].

The procedure of transplantation is the gold standard of therapy for individuals with end-stage organ failure since it bolsters survival and promotes life quality [10,11]. For the first two decades after organ transplantation became a clinical option, acute allograft rejection was the primary barrier to success. The development and application of immunosuppressive medicines have led to significant advancements. Graft survival at one year with current immunosuppressive medications surpasses 90% in most sites [12].

Kidney transplantation has advanced to the point where it is now the treatment of choice for ESRD patients. Patient and graft survival rates are impressive, typically yielding great short- and medium-term results, but long-term renal graft survival has not improved. Patients with ESRD have better survival rates after a kidney transplant than they do after receiving dialysis treatment [7]. On the other hand, pre-transplant dialysis treatment and concomitant medical conditions contribute to the high death rate in renal transplant recipients. CAN, defined as a slow loss in kidney function, is influenced not only by conventional risk factors but also by oxidative stress [13,14]. Although transplanting kidneys is successful in recovering renal function, it does not fully address underlying disease causes like chronic low-grade inflammation and continuous redox imbalance [15].

Among the many variables that may contribute to chronic kidney transplant problems, immunosuppressive treatment plays a role. There is an upsurge in oxidative phenomena associated with endothelial dysfunction, inflammation, and atherosclerosis following a kidney transplant. These factors lead to graft deterioration and cardiovascular problems, which are a leading cause of patient mortality. The prooxidant effects of calcineurin inhibitors have been applied in a variety of experiments [7]. In contrast to Tacrolimus (FK506), Cyclosporine (CsA) has only been cited as the more potent inducer of oxidative stress [16,17].

Excessive reactive oxygen species (ROS) development is oxidative stress's fundamental mechanism. The most prevalent factors causing ESRD, hypertension, and diabetes produce excessive ROS in artery walls [18]. This is the underlying cause of vascular inflammation and endothelial dysfunction-induced arterial remodeling and atherogenesis. The hemodialysis technique and aging during the pretransplant phase will also have an impact on the quality of the vessels. Undoubtedly, the transplant lowers the level of uremic toxins, which contribute to inflammation; yet, the process and the ensuing immunosuppressive medication may also contribute to an increase in oxidative stress [7].

2-Calcineurin inhibitors (CNIs)

To this day, CNIs are considered the gold standard of treatment in the life-saving field of organ transplantation. In the four decades since cyclosporine's discovery [19,20], Ninety percent or more of kidney transplant patients received immunosuppressive CNIs in 2017. Beyond transplanting, CNIs are being researched and applied to treat immune-mediated glomerular disorders [21].

2.1. Discovery of CNIs

It was the collaborative efforts of scientists at Sandoz (now Novartis) that led to the development of CsA, a major advance in modern medicine. More than three decades after its discovery, it is still widely used because of the enormous improvement it brought to the outcome of organ transplant recipients [19].

Cyclosporine was first extracted from *Tolypocladium inflatum* in 1971. Animal studies on its immunosuppressive effects were published in 1976, and by 1979, Sir Roy Calne at Cambridge University had shown its benefits to transplant recipients in the clinic. In 1983, the United States Food and Drug Administration (FDA) gave CsA the green light for utilization in kidney transplant patients [21].

After ten years, Fujisawa Pharmaceuticals scientists identified another drug from *Streptomyces tsukubaensis*, which they coded FK506 and named tacrolimus [19,22].

2.2. Pharmacokinetics of CNIs

Cyclosporine plus FK506 may be delivered sublingually, intravenously, or orally (PO). The area under the curve for PO CNIs varies by up to 50 percent amongst patients, depending on factors such as formulation, time, and concurrent food administration. CNIs are plasma protein-bound, lipophilic, and widely distributed after administration. CYP3A mediates hepatically mediated metabolism, and metabolites are eliminated in the bile with a 10–48-hour elimination half-life. By contrast to CsA, whose metabolites have only 10 to 20% of the parent drug's activity, FK506's

therapeutic effects are sustained by a robust metabolite that equals its immunosuppressive abilities. CsA microemulsion (Neoral ®) enhances medication exposure by 34% and oral bioavailability (faster and higher peak, around 67 percent) [21,23]. An increased prevalence of CNI-related nephrotoxicity may potentially be caused by polymorphisms that cause CYP3A5 to lose function. CNI content in tubular epithelial cells of the kidney, oral bioavailability, and drug clearance may be affected by mutations in ABCB1 that encode the efflux transporter P-glycoprotein [21].

2.3. Pharmacodynamics of CNIs

Tacrolimus and CsA exhibit identical pharmacologic characteristics of inhibiting calcineurin to decrease activated T cells [19]. Their therapeutic window is small; at low levels, there is an increased acute graft failure risk; at high levels, there is an increased risk of nephrotoxicity, which can result in acute or chronic kidney allograft injury. Regrettably, there is a dearth of real-time biomarkers that can be used to evaluate the pharmacodynamic effectiveness of CNIs. Regular clinical evaluation for drug or immune-related adverse effects, that can point to hypo- or hyper-immunosuppression, is used to assess CNI pharmacodynamic dosage sufficiency [21].

2.4. Structure and the mechanism of action of CNI*s*

Cyclosporine, a highly lipophilic cyclic endecapeptide containing N-methylated amino acids, is effective as an oral immunosuppressant because it is not inactivated by gastric acid. CsA from the fungus binds cyclophilin. The CsA-cyclophilin complex blocks calcineurin. Calcineurin is divided into two subunits: A, which maintains its phosphatase activity as the catalytic subunit (CnA), and B, which modulates CnA activation and is incredibly sensitive to intracellular calcium. T cell activation via TCR receptor stimulation increases intracellular calcium and activates CnB, which triggers CnA's phosphatase activity. Active CnA dephosphorylates cytoplasmic nuclear factors of activated T cell (NFATc), a transcription factor, that translocates into the nucleus with activated calcineurin and upregulates the expression of several cytokines and costimulatory molecules needed for complete T cell activation [12,19,23].

Tacrolimus is one type of macrolides. It possesses a similar high solubility in lipids and other organic solvents, despite being more soluble in water than CsA. The cytosolic immunophilin blocked by FK506 is called FKBP-12 (FK binding protein). The FK506-FKBP complex also inhibits the enzyme calcineurin. By inhibiting calcineurin, both drugs CsA and FK506 block the transcription of NFATc. The result is that T cells are maintained in a resting state because T-cell stimulation signals do not result in the transition of G0 to G1 of the cell cycle. In addition, blocking calcineurin prevents the production of a wide variety of cytokines [12,19,22,23].

2.5. Nephrotoxicity of CNIs

Nephrotoxicity is the situation in which the kidneys cannot properly detoxify and eliminate medications and harmful compounds due to their destruction or injury. Drugs, chemicals, and environmental toxins all play a role in causing this condition. An estimated 25% of nephrotoxicity is attributable to medications; this number rises to as high as 66 % in the elderly [2].

2.5.1. Epidemiology of CNIs nephrotoxicity

About 17% and 50% of people who get kidney transplants have acute CNI nephrotoxicity. CsA and FK506 recipients had 22.6 and 19.8% acute nephrotoxicity, respectively. The risk increased with all organ transplants and was 7–21% five years post-transplant. The mortality risk for those experiencing CNI renal toxicity was 4.6 times greater than those without CKD [24].

2.5.2. Pathophysiology and Types of CNIs nephrotoxicity

There are two different types of nephrotoxicity: acute, reversible, and chronic, resulting in significant damage. Because of vasoconstriction in both the afferent and efferent arterioles, reduced GFR has a hemodynamic effect. This action may depend on endothelin-induced renin-angiotensin-aldosterone system activation. Endothelial dysfunction is also linked to CNIs due to increasing thromboxane generation and decreasing nitric oxide and prostaglandin E2 synthesis. In vitro, the toxicity of CsA to the tubules has been established [23]. Reversible vasoconstriction of afferent arterioles is the primary mechanism behind acute CNI nephrotoxicity; however, tubular injury, thrombotic microangiopathy, and hemolytic uremic disorder were additionally observed [24].

Histological changes such as arteriolar hyalinosis, interstitial fibrosis, "striped" tubular atrophy, and glomerulosclerosis are indicative of persistent irreversible nephrotoxic consequences. Increased levels of transforming growth factor beta1

(TGF-β_1) and angiotensin II, P-glycoprotein inhibition, and activation of apoptosis of tubular epithelial cells in the kidney are responsible for the sustained hemodynamic effects [23].

2.5.3. Cyclosporine nephrotoxicity VS FK506 nephrotoxicity

Both CsA and FK506 induce acute and chronic nephrotoxicity. Nevertheless, FK506 exhibits reduced nephrotoxicity at reduced dosages while maintaining efficacy. Furthermore, in non-kidney transplant patients, the prevalence of late-onset hypertension and early-onset acute renal damage was comparable with FK506, whereas late CKD was more prevalent with FK506. CKD in these patients may, nevertheless, be attributable to factors other than CNI renal toxicity. Interestingly, multiple studies found that FK506 reduced liver transplant nephrotoxicity and had similar effects on other organ transplants. In animal and human research, CsA causes more vasoconstriction than FK506. CsA also exacerbated acute nephrotoxicity over FK506 [24,25].

2.5.4. Risk factors of CNIs nephrotoxicity

Older kidney donors and systemic exposure to Excessive dosages of CsA or FK506 may increase CNI kidney damage risk [26]. Drug interactions, salt depletion, and diuretic use were identified as local susceptibility factors for CNI renal toxicity, as were the concurrent use of nephrotoxic drugs (such as nonsteroidal anti-inflammatory drugs) and cytochromeP-450 3A4/5 inhibitors (such as ketoconazole) that enhance exposure to CNI metabolites, drugs that interfere with ABCB1-mediated transport in the tubular epithelial cells (such as mammalian target of rapamycin (mTOR) inhibitors), and treatments that block P-glycoprotein mediated efflux of CNIs from tubular epithelial cells (such as amiodarone and proton pump inhibitors) that increase local renal exposure to CNIs [19,24].

3. The molecular mechanism of CNIs- induced nephrotoxicity

3.1. CNIs- induced alterations in kidney function_

The most reliable markers of renal disease, as shown by the exploratory study, are SCr, blood urea nitrogen (BUN), and kidney weight/body index. High levels of BUN and SCr have been identified as vital predictors of renal failure (glomerular injury markers) [3,27]. Renal function declined due to CNI nephrotoxicity, as BUN and SCr levels increased significantly [28].

3.2. Effect of CNIs nephrotoxicity on mitochondrial function

Nevertheless, the administration of T-cell suppression medicines is necessary for foreign tissue to be accepted. Increasingly, the importance of cell metabolism in T-cell development, function, and activation is acknowledged. T-cells create their adenosine triphosphate (ATP) predominantly through mitochondrial oxidative phosphorylation pathways, but upon activation, they switch to using more glycolysis (a phenomenon known as the "Warburg effect"). A reduction in mitochondrial membrane potential, mitochondrial swelling, as well as the release of cytochrome c are all revealed in kidney tubule cells treated with CsA. The development of the mitochondrial transition pore is blocked by CsA, allowing mitochondrial cytochrome c to be released into the cytoplasm and starting the apoptotic cascade [29,30]. In general, immunosuppressive medications that disrupt mitochondrial function may hinder T-cell development and function by lowering energy production, creating harmful ROS, and causing apoptosis [16,30].

3.3. CNIs- induced oxidative stress_

A condition in which oxidant production and antioxidant defense are out of balance constitutes oxidative stress, which impacts early post-transplantation results and graft health. Due to this imbalance, morbidity and mortality risk, and chronic allograft nephropathy, which causes kidney function to deteriorate, develops [7,9,31].

The numerous mitochondria of renal tubular epithelial cells provide ATP for the reabsorption of water and solutes from urine. ROS from mitochondrial respiration reacts strongly with biomolecules. Low ROS are necessary for kidney homeostasis, whereas excessive ROS cause oxidative stress in renal cells [1,32]. The oxidative stress inducer CsA is stronger than FK506 [7]. About 20–25 percent of cardiac output flows to the kidneys to be oxygenated by blood flow. Some arterial-to-venous shunts in the renal vasculature generate erratic blood flow. During the period of reperfusion, ROS are generated by the mitochondrial respiration chain and/or nicotinamide adenine dinucleotide phosphate (NADPH) oxidases. Furthermore, the buildup of electrophilic molecules results in oxidative stress. This is caused by shear stress in blood flow and activates nuclear factor erythroid-2related factor2 (Nrf2) in endothelial cells. Thus, oxidative stress mitigation is a key therapeutic target for renal disease prevention [1].

Excess ROS and electrophiles cause oxidative stress, cell death, inflammation, and fibrosis. Locally activated renal microenvironments or hematopoietic organ-migrating inflammatory cells generate ROS. Oxidative stress, along with inflammation, appears to be a major cause of AKI and CKD, which includes diabetes, hypertension, and nephropathy [1,31].

3.3.1. Antioxidant enzymes

Considering the rise in ROS generation. Catalase (CAT), superoxide dismutase (SOD), glutathione (GSH), glutathione reductase (GR), and glutathione peroxidase (GPx) are all antioxidant enzymes whose activity is diminished. These ROS also play a role in proteinuria, inflammation, fibrotic alterations, and altered renal blood flow [28,33-35].

3.3.2. Oxidative stress marker Malonyl dialdehyde (MDA)

When ROS are generated by CNIs, they engage with macromolecules in the cell (lipids, proteins, and DNA). These ROS hasten the processes of protein denaturation and DNA damage. ROS furthermore causes polyunsaturated fatty acid peroxidation (PUFAs) and MDA formation, which is a marker of cell membrane lipid peroxidation. These factors caused cellular injury and necrosis [28,34].

3.3.3 NOX expression

The mitochondrial enzymes NADPH oxidase (NOX) and xanthine oxidase (XO) are responsible for catalyzing the production of ROS like superoxide anion (O2-), hydrogen peroxide (H2O2), and hydroxyl radicals (OH). Renal Nox4 is best defined among NOX family members. In response to renal injury, podocytes, mesangial cells, and endothelial cells increased Nox4, which accelerated kidney disease progression [9,16,35].

3.3.4. Inducible nitric oxide synthase (iNOS)

Nitric oxide synthase (NOS) is essential for producing NO, peroxynitrite ($ONOO^-$), nitrotyrosine, and nitroso thiols. Triple isoforms of NOS exist in neuronal NOS (nNOS) plus endothelial NOS (eNOS), which are constitutively expressed by central and peripheral neurons and endothelial cells, respectively. Furthermore, inflammation triggers the production of inducible NOS (iNOS). Glomeruli in a normal kidney express eNOS but not nNOS, while cortical tubules express nNOS but not eNOS. In CKD animal models, increased iNOS in kidney injuries was linked to inflammation [9,28].

3.3.5. NrF2/HO-1

By activating and influencing the expression of many antioxidant enzymes like NADPH, NAD(P)H: quinone oxidoreductase 1 (NQO1), heme oxygenase-1 (HO-1), and others, Nrf2 helps preserve cellular homeostasis, minimizes cellular injury from redox imbalance, and keeps up the dynamic balance of systematic oxidation and reduction consequences. Furthermore, through its modulation of oxidative stress and inflammation, HO-1 may buffer non-specific damage after AKI or CKD. One of its main tasks is to break down heme (Fe-protoporphyrin IX) into free iron, carbon monoxide (CO), and biliverdin, which is swiftly converted into bilirubin [1,3,35].

The Nrf2/HO-1 pathway greatly reduces renal pathological oxidative stress. Increased renal oxidative stress and inflammation are the results of CNIs' suppression of Nrf2/HO-1 signaling pathway in the kidney, inhibition of renal Nrf2 activation, and suppression of Nrf2 gene expression [1,2,9,36].

3.4. CNIs- induced inflammation

Inflammation is integral to the onset and progression of renal fibrosis. The inflammatory microenvironment includes pro-inflammatory cytokines, bone marrow-derived inflammatory cells, and nearby injured kidney cells. The most well-known immune cells in renal inflammation are macrophages. Two extreme macrophage phenotypes are M1 and M2. M1-proinflammatory macrophages generate free radicals, tumor necrosis factor-alpha (TNF-α), and interleukin-1β to promote inflammation and generate AKI. The M2 phenotype triggers the release of anti-inflammatory cytokines such as interleukin-10 and insulin-like growth factor-1 to withstand acute inflammation. Although M1 macrophages play a key role in chronic inflammation and renal degeneration, M2 macrophages cause excessive ECM deposition. Macrophages effectively activate myofibroblasts by producing growth factors such as TGF-β_1. They harm endothelial cells and aggravate hypoxia impairment [9,35].

3.4.1. NF-κB

A class of eukaryotic transcription factors called nuclear factor-kappa beta (NF-κB) is critical to the successful inflammatory process as well as the synthesis of pro-inflammatory components, such as cytokines, and enzymes like cyclooxygenase-2, iNOS, TNF-α, and interleukin-6. Besides that, genes involved in cell division, differentiation, and death are expressed under the regulation of NF-κB [3,9,34,35,37]. Angiotensin II and TNF-α are significant triggers for NF-κB activation. Once TNF-α binds to

the receptor, NF-κB is activated. Elevated levels of nephrotoxicity from CNIs are associated with upregulation of the NF-κB cascade in the kidneys [2,9,37].

3.4.2. P38-MAPK

The P38 mitogen-activated protein kinase (MAPK) signaling chain is thought to be both pro-apoptotic and pro-inflammatory, making it a key MAPK family member. P38-MAPK modulates a wide variety of immune and inflammatory genes [3,9]. High levels of p38-MAPK in the kidney are linked to CNI-induced renal damage [2].

3.4.3. TGF-β_1/Smad pathway

Typically, TGF-β_1 is released as a latent complex with covalently attached latent TGF-β_1 binding proteins (LTBP). Both proteolytic and nonproteolytic processes can activate TGF-β_1. In this regard, the latency-associated peptide can undergo structural change due to oxidation, resulting in TGF-β_1 release. Upon activation, TGF-β_1 connects with receptors to initiate biological activity, causing Smad phosphorylation. Following phosphorylation, Smads connect to Smad 4 to create a complex that transmits to the nucleus to stimulate several specific genes, which include the tissue inhibitors of metalloproteinases-1 (TIMP-1) and connective tissue growth factor (CTGF). CNIs promote TGF-β_1/Smad signaling in renal mesangial cells, a ROS-dependent process [9,12,23,35].

3.4.4. Toll-like receptor signaling

Toll-like receptors (TLRs) are a type of cytoplasmic pattern recognition receptors (PRRs). Ten different isoforms of TLRs exist in humans. When TLRs are activated, NF-κB is turned on. TLR activation, particularly TLR4, and TLR2 leads to renal cell damage, immune cell recruitment from bone marrow, and upregulation of inflammatory molecules Like interleukin-6, interleukeine-8, and interleukeine-1β via NF-κB and MAPK signaling [9,35,38]. The higher expression of TLRs in the kidneys is linked to CNIs [38,39].

3.5. CNIs- induced apoptosis

Mitochondrial membrane depolarization and loss of mitochondrial membrane potentials (MMPs) are thought to be the initial stage in the mitochondria-mediated intrinsic apoptosis pathway, both of which are caused by an excess of ROS. Moreover, mitochondrial dysfunction impairs intracellular ATP synthesis by causing irregularities within mitochondrial respiratory chain electron transport channels. Components of the B-cell lymphoma-2 (Bcl-2) family, which includes both anti- and pro-apoptotic proteins, have a role in controlling the stimulation of mitochondria-mediated apoptosis. Bcl-2 on the outer mitochondrial membrane prevents apoptogenic substances from releasing. However, pro-apoptotic proteins like Bcl-2 associated x protein (Bax) oppose anti-apoptotic proteins or translocate to the mitochondrial membrane to form membrane-integrated homo-oligomers that produce mitochondrial pores, lose MMP, and release cytosolic apoptotic agents. In conclusion, the intrinsic apoptosis process is activated or inhibited by the balance between Bax and Bcl-2 proteins. Tacrolimus-induced apoptosis was linked to decreased Bcl-2/Bax ratio and/or caspase-3 activation in previously preclinical studies. Hence, it has been established that many naturally occurring compounds possessing antioxidant qualities offer protection against the cytotoxicity caused by tacrolimus in addition to the decline in the Bcl-2/Bax ratio and/or caspase-3 activation [16,29,30,34].

4. CNIs nephrotoxicity mitigation and prevention strategies

Avoidance, reduction, and conversion to the mTOR dosage of CNIs were all attempts to lessen or eliminate the nephrotoxicity seen in some patients taking these drugs. Patients with anti-hepatitis C virus antibodies, those who are elderly, overweight, or obese, and those who have many risk factors at once should all have their starting dose of FK506 lowered [40].

4.1. CNIs avoidance

Several randomized controlled trials (RCTs) have examined immunosuppressive regimens that utilize sirolimus or belatacept instead of CNIs [24,41,42]. Belatacept is a blocker of CD80/86-CD28 co-stimulation that does not cause kidney damage. Additionally, belatacept reduces the risk of cardiovascular complications (such as hypertension and dyslipidemia) linked to CNI [7,12,24,38]. In patients receiving kidney transplants who have renal failure as a result of CNI toxicity, belatacept has been suggested as a potential first-line treatment [38,43-45].

4.2. CNIs minimization

Several RCTs utilizing CsA, FK506, and combining either of those were recognized as evaluating dosage minimization for CNI [24,41]. These investigations revealed that CNI reduction enhanced renal function and reduced graft loss. They also showed lower viral infection rates and no mortality differential [41].

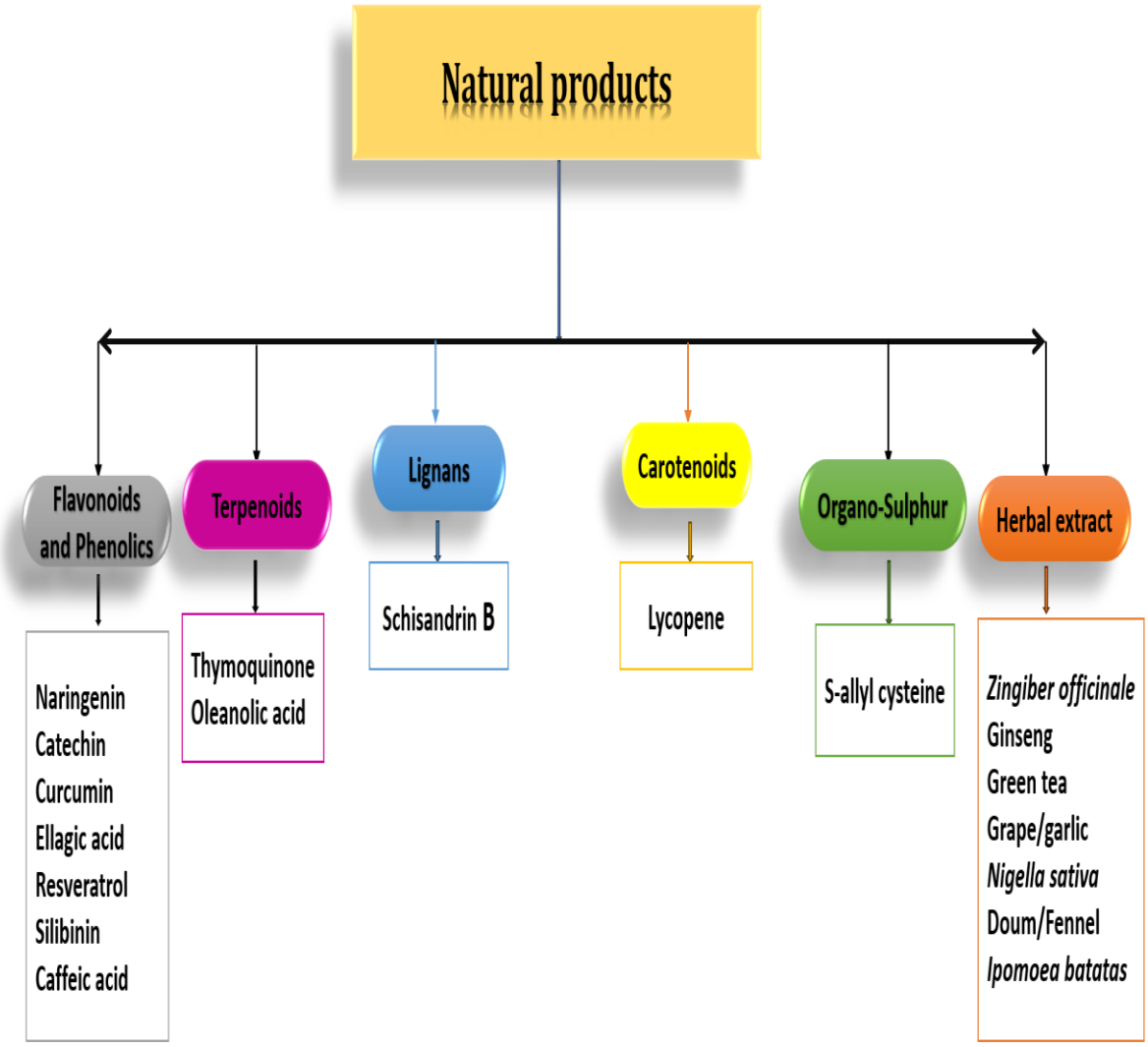

Figure 1. Several groups of natural compounds protect against CsA-induced kidney injury.

4.3. CNIs conversion

In the bulk of studies that have investigated CNI-to-mTOR inhibitor conversion within three to six months of the transplant, most investigations found that conversion had taken place. Moreover, switching to a mTOR inhibitor has been linked to a decreased incidence of reported viral infections [41,46].

4.4. Nanoparticles delivery system of FK506

Nanoparticles (NP) consisting of the biodegradable copolymer poly (lactic-*co*-glycolic acid) (PLGA) have been given the green light for use in medicine by the FDA and the European Medicines Agency (EMA). The PLGA NPs formulation offers a promising substitute for the standard FK506 formulation. Consequently, nephrotoxicity may be mitigated while FK506's immunosuppressive effects are preserved. When compared to immediate-release FK506 capsules, the newly designed approach increased FK506 blood levels and lengthened circulation time [24,47,48].

4.5. Protective effects of natural compounds against nephrotoxicity from cyclosporine

Various natural biomolecules have been discovered to lessen or alleviate the degree of kidney damage caused by CsA [2] (**Figure 1**).

5. CONCLUSIONS

On the one hand, CNIs are the savior and the Achilles' heel of renal replacement therapy. Renal transplant recipients may be plagued by the many toxicities of CNIs, even though these drugs greatly decrease the likelihood of acute rejection. CNI nephrotoxicity will be evident in nearly all allografts within a few years. There is substantial evidence linking CNIs to post-transplant hypertension, dyslipidemia, and the development of diabetes, all of which considerably increase the recipient's cardiovascular risk. CNI-induced nephrotoxicity implies high renal oxidative stress, renal inflammatory reactions, destruction, apoptosis, and abnormal signaling. Nephrotoxicity caused by CNIs can be mitigated with the use of reno-protective pharmaceuticals. These drugs include ROS scavengers, powerful direct or indirect antioxidants, and cellular anti-inflammatory agents.

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