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Nephroprotective activity of medicinal plants: A review on *in silico*-, *in vitro*-, and i*n vivo*-based studies

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ABSTRACT

Acute kidney injury (AKI) is a severe problem for healthcare professionals due to its high mortality rate. The major causes of AKI are ischemia, hypoxia, and drug-induced nephrotoxicity. AKI is particularly related to an imbalance between oxygen and nutrients, which is caused by impaired circulation to the nephrons and increased energy requirements due to oxidative stress. Thus, the concept of using antioxidants to prevent AKI is always interesting to be thoroughly discussed. Many plants have been well recognized for their antioxidant properties, which providentially could work to recover AKI. This review focuses on plants with nephroprotective activity as confirmed by *in silico*, *in vitro*, and *in vivo* studies. *In vitro* and *in vivo* nephroprotective studies of several plants on *Combretum micranthum*, *Homonoia riparia*, *Abelmoschus moschatus*, *Asparagus falcatus*, *Barleria prionitis*, *Macrothelypteris oligophlebia*, *Solanum xanthocarpum*, *Sonchus oleraceus*, *Ceiba pentandra*, *Eurycoma longifolia*, *Dendropanax morbifera*, *Carica papaya*, and *Boesenbergia rotunda* reveal promising results. Moreover, *in silico* studies of phytoconstituents against nuclear factor κB, the most important components of the pathogenesis of AKI, confirm scientific evidence that plants are potential candidates to be developed as nephroprotective drugs.

INTRODUCTION

The kidneys are organs that play an essential role in the human body. In general, the kidneys function in several ways in the body, including acid-base balance, regulation of the endocrine system, blood pressure, and erythropoiesis (Al-Snafi & Talab, 2019). Abnormality in the kidneys will interfere with the regulatory function and change the homeostasis, which can be life-threatening (Dhondup & Qian, 2017). The Global Burden of Disease stated that nearly 1.2 million people die from kidney failure. This increased by 32% over the period of 2005–2015 (Luyckx *et al*., 2018), whereas according to GLOMMS-II and multinational databases, about 8%–18% or 22% of hospitalized patients are diagnosed with acute kidney injury (AKI). Most of these patients developed AKI within 2 days of being admitted to the intensive care unit (Hansrivijit *et al*., 2021).

Medication, such as anticancer drugs, is a common cause of kidney injury. The current drug-induced nephrotoxicity focuses on AKI. A prospective cohort study related to AKI due to drug exposure showed that the incidence of nephrotoxicity in adults was around 14%–26%, whereas 16% occurred in the hospital's pediatric population. These incidents are more common in inpatients, especially intensive care patients (Perazella, 2018). The AKI incidence is a severe problem for healthcare professionals due to its high mortality rate (Kirkley *et al*., 2019; Park *et al*., 2018; Winther-Jensen *et al*., 2018).

AKI is a reversible condition with a sudden decrease in kidney function, an increase in serum creatinine and blood urea nitrogen, and a reduced-glomerular filtration rate (GFR) (Konda *et al*., 2016). AKI can develop into chronic kidney disease (CKD) if it is not detected or treated early. At the end-stage renal disease level, this is a severe condition that requires kidney transplantation or dialysis (Cho *et al*., 2018). Moreover, it can be defined that AKI is particularly related to an imbalance between oxygen and nutrients,

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which is caused by the occurrence of impaired microcirculation to the nephrons and increased energy requirements due to oxidative stress in the cells (Makris & Spanou, 2016). However, the concept of using antioxidants to prevent AKI is always interesting to be thoroughly discussed. This review focuses on plants with nephroprotective activity as confirmed by *in silico*, *in vitro*, and *in vivo* studies.

METHODS

Literature search was carried out by using the National Center for Biotechnology Information database with the following keywords: "nephroprotective activity" [Medical Subject Headings (MeSH) terms] or "medicinal plants" [all fields] and ("plants, medicinal"[MeSH Terms] or ("plants"[All Fields] and "medicinal"[All Fields]) or "medicinal plants"[All Fields] or ("medicinal"[All Fields] and "plant"[All Fields]) or "medicinal plant"[All Fields]) and ("computer simulation"[MeSH Terms] or ("computer"[All Fields] and "simulation"[All Fields]) or "computer simulation"[All Fields] or "*silico*"[All Fields] or "*in silico*"[All Fields]) and ("*in vitro* techniques"[MeSH Terms] or ("*vitro*"[All Fields] and "techniques"[All Fields]) or "*in vitro* techniques"[All Fields] or "*vitro*"[All Fields] or "*in vitro*"[All Fields]) and (("in"[All Fields] and "*vivo*"[All Fields]) or "*in vivo"*[All Fields]) and "studies"[All Fields]. Additional references as supporting scientific data were searched using the same keywords.

PATHOPHYSIOLOGY OF AKI

The pathophysiology of AKI is multifactorial and complex, where the most widely recognized causes are ischemia, hypoxia, and nephrotoxicity (Basile *et al*., 2012). These causes are very influential on the kidneys resulting in vasoconstriction, endothelial damage, and activation of the inflammatory process. This impact affects the tubular blood vessels in the outer medulla of the kidney, where the partial pressure of oxygen becomes low, resulting in decreased renal blood flow (RBF) (Basile & Yoder, 2014). In a similar manner, serum or plasma creatinine affirmation is comprehensively used for AKI confirmation, yet there is a nondirect association between creatinine obsession and GFR (Thuraisingham & Adu, 2013). The increase in blood creatinine after AKI was due to a 90% decrease in creatinine clearance from baseline (Waikar & Bonventre, 2009).

During ischemia, AKI is specified into five phases (as shown in Fig. 1), which starts from the first phase, namely, the prerenal phase. The prerenal phase continues to the next stage if the RBF decreases but the cellular stability is maintained. Subsequently, the second phase, namely initiation, is characterized by a decrease in GFR due to decreased net ultrafiltration pressure. Ischemic injury is more concentrated in the S3 segment of the proximal tubule due to the high use of ATP in the area, resulting in a lower oxygen partial pressure. Moreover, ischemia causes ATP depletion, blocks sodium transport, produces reactive oxygen species (ROS), causes changes in cytoskeletal structure, and causes loss of cell polarity. The third phase is an extension, where a change in the structure and function of vascular endothelial cells and renal tubular epithelium occurs, resulting in the recruitment of inflammatory cells, including neutrophils, lymphocytes, and macrophages, as well as the expression of adhesion molecules

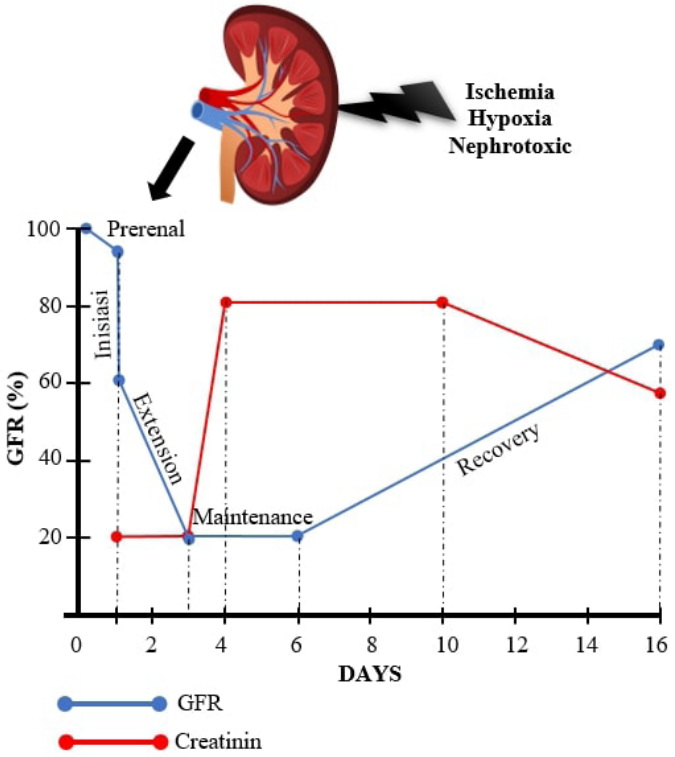

Figure 1. The relationship between GFR and serum creatinine (SCr) in the AKI phase. Adapted and modified from (Seller-Pérez *et al*. (2016), Sutton *et al*. (2002), and Mattei *et al*. (2016).

and chemokines. S3-segment cells activate proinflammatory gene transcription via interferon-1 regulatory factor. On the other hand, proximal tubular cells producing cytokines (TNF-α, TGF-β, and interleukin), including IL-18 and IL-6, are also released into the tubular lumen and can be used as early markers of kidney damage. The following fourth phase is maintenance, which lasts for 1 or 2 weeks and usually occurs in oliguria and uremic. In addition, GFR during this phase is stabilized at the lowest level after reperfusion. Consequently, the cells undergo repair, migration, apoptosis, and proliferation in the efforts of cellular and tubule stability. The last phase is recovery; gradually in this phase, there are repair and regeneration of the tubular epithelium, as well as GFR toward a normal state (Hoste *et al*., 2015).

DRUGS THAT INDUCE AKI

NSAIDs

NSAIDs, selectively or not, inhibit the arachidonic acid cascade, resulting in a nonpermissive effect on prostaglandin formation. In the kidney, prostaglandins, especially prostacyclins, PGE2, and PGD2, will act as vasodilators in afferent arterioles, increasing renal perfusion, by distributing cortical flow to nephrons in the medulla region of the kidney (Lucas *et al*., 2018). This vasodilation acts as a negative feedback on the mechanisms, such as the performance of the renin–angiotensin–aldosterone system and the sympathetic nervous system, culminating with compensation to ensure adequate flow to the organ. NSAIDs inhibit this mechanism and can cause acute vasoconstriction and spinal cord ischemia, which can lead to AKI (Palmer *et al*., 2008).

ACE inhibitors

ACEIs are the most commonly used cardiovascular drugs for hypertension treatment; however, these drugs cause mild renal insufficiency due to decreased GFR (Muneer & Nair, 2017). Such defects occur because the vasoconstriction of the efferent arterioles that depends on angiotensin II is essential for maintaining intraglomerular capillary pressure (Rolland *et al*., 2021; Stirling *et al*., 2003). Blockade of the angiotensin–renin system leads to a sharp decrease in GFR. Besides, the drug can cause severe hyperkalemia in patients using beta-blockers, NSAIDs, or potassium-sparing diuretics (Caires *et al*., 2019).

Cisplatin

Cisplatin induces AKI through various pathways and molecular mechanisms, including cellular absorption and accumulation, inflammation, oxidative stress, vascular injury, endoplasmic reticulum stress (ER), and necrosis and apoptosis (McSweeney *et al*., 2021). Cell death and inflammation are found mainly in the proximal tubule segment of nephrons, where there is a high accumulation of cisplatin. Morphological analysis of cisplatin nephrotoxicity shows that most cell damage to the renal tubules is caused by necrosis (Xu *et al*., 2015). This leads to increased renal vascular resistance and decreased renal plasma flow and GFR (Ozkok & Edelstein, 2014).

Aminoglycoside antibiotics

Aminoglycoside antibiotics (AG) are widely used in the treatment of various infections, for example, eye, pulmonary, and intestinal infections, which are produced by Gram-negative bacteria and bacterial endocarditis. The number of amino groups and the distribution of molecules in the cationic structure have an important role in their toxicity to kidney tissue (Lopez-Novoa *et al*., 2011). In its free form, the AG crosses the glomeruli, further absorbed and well-penetrated into the proximal convolution tubules (Ong *et al*., 2016). It can affect nephrons at glomerular and tubule levels. AG-exposed glomerulus lowers surface area for ultrafiltration process, basal membrane thickness increases, and glomerular deformation and number and diameter of fenestrae are reduced (Prayle *et al*., 2010).

THE ROLE OF NUCLEAR FACTOR-KB (NF-KB) SIGNALING PATHWAY IN AKI

NF-κB was at first found as a B-cell nuclear protein restricting to the κ enhancer of the immunoglobulin κ light chain quality (Zhang & Sun, 2015). NF-κB activation mediates two main signaling lines, namely, canonical and noncanonical pathways (Vallabhapurapu & Karin, 2009; Sun, 2010). The canonical path relies on the multisubunit inhibitors (IκBs) kinase (IKK), consisting of two catalytic subunits, IKKα and IKKβ, and a regulatory subunit named NF-κB essential modulator or IKKγ (Adli *et al*., 2010; Israël, 2010). Canonical signaling members of NF-κB include p50/NF-κB1, p65/RelA, and c-Rel, with the most common dimers being p50/NF-κB1-p65/RelA and p50/NF-κB1-c-Rel (White *et al*., 2020). In physiological conditions, NF-κB is isolated in the cytoplasm in a complex with NF-κB IκBs. When there are specific stimuli, the complex will be phosphorylated and will produce ubiquitination and degradation of the IκB, resulting in the translocation of the free NF-κB to the nucleus. In the promoter area, NF-κB will bind to a specific sequence that leads to the proinflammatory effect or encoding gene, as well as the IκB protein to restore a stable state. The heterodimer p65–p50 (NF-κB) is most commonly activated by various stimuli relevant to kidney injury, including cytokines and growth factors, pathogen-related damage, and metabolic stress (Markó *et al*., 2016).

Activation of NF-κB in kidney injury is caused by ischemia-reperfusion, where the kidneys are in a hypoxia condition and have low RBF. Inflammation caused by AKI is an essential factor that exacerbates kidney injury, and inflammation control is effective for minimizing kidney injury and speeding recovery (Sanz *et al*., 2010). Inflammation occurs starting from the activation of the signaling of various pathways that regulate the expression of pro- and anti-inflammatory mediators in tissue cells and leukocytes. These signalings have been known to come from members of the IL-1 and TNF receptor families, as well as Toll-like microbial pattern recognition receptors, which belong to the families IL-1R, IL-1, and TNFα released immediately after tissue injury or infection (Lawrence, 2009).

In *in vivo* studies, it has been reported that inhibition of NF-κB may result in a decrease of inflammation of the kidneys (Fujihara *et al*., 2007; Volpini *et al*., 2004). NF-κB has been known to likewise be engaged with the pathogenesis of kidney harm brought about by hypertension. A study revealed that NF-κB is a key in the regulation of kidney injury, where the findings prove that inhibition of NF-κB can weaken progressive kidney damage in rat models of hypertension and kidney injury due to aldosterone/salt (Ding *et al*., 2012).

Another study proved that the suppression of NF-κB in endothelial cells stops the signaling cascade leading to a decrease in kidney damage due to hypertension (Henke *et al*., 2007). Other studies have also reported that NF-κB activation could increase inflammation in angiotensin-II-induced mice (Müller *et al*., 2000). Inhibition of IKKβ expression and activation of NF-κB in ischemia-reperfusion rats with induction of renal arterial clamping has been reported, where the administration of local SIRNA IKKβ results in the inhibition of the expression of the kidney IKKβ gene, binding activity of NF-κB/DNA (Wan *et al*., 2011). Moreover, expanded articulation of kidney, relA, NF-κB2, and p53 qualities was confirmed in high-portion folic corrosive instigated AKI mice; results propose that NF-κB assumed a significant part in keeping up kidney work which additionally elaborates setting p53 levels during AKI (Kumar *et al*., 2015). Therefore, understanding the mechanism of NF-κB regulation is very important for the future state of AKI treatment.

Interestingly, a recently published work by Razak *et al*. (2021) revealed that the cavity of NF-κB consists of key amino acid residues, e.g., Lys244, Arg57, Ser243, Arg59, Ser249, Lys275, Gln309, and Phe310. An inhibitor of NF-κB should be able to interact with these residues either by building covalent bonds or by pi–pi interactions. Furthermore, hydrogen bonds with Gln220, Arg30, and Phe184 are also favorable to increase the affinity of the inhibitor.

PLANTS WITH NEPHROPROTECTIVE ACTIVITY: *IN VITRO* AND *IN VIVO* STUDIES

It has been proven that plants with nephroprotective activity can reduce the toxicity of drugs when both were taken together (Gaikwad *et al*., 2012). Nephroprotectors are compounds capable of minimizing nephrotoxic effects. Plants

have nephroprotective activity, due to various complex chemical substances (Chinnappan *et al*., 2019). Many studies have been carried out to scientifically prove that plants can be used to treat kidney disease. Flavonoids are secondary metabolite compounds in plants that have an essential effect on kidney physiology, including nephroprotective (Vargas *et al*., 2018)

Flavonoids are classified as the polyphenol group. There is a benzopyrone structure in the compound, which is widely contained in various plants. This compound is the result of synthesis from the phenylpropanoid pathway (Kumar & Pandey, 2013), which has been known to have many pharmacological activities due to its antioxidant effects (Wang *et al*., 2018). Recent information on the impact of flavonoids on renal function and the mechanisms of action involved suggests that flavonoids have an essential effect on renal physiology and have diuretic and natriuretic properties, as well as exerting a renoprotective influence in AKI and CKD of various etiologies, including hypertension, diabetes, nephrotoxicity, and stress oxidative agents (Vargas *et al*., 2018).

Quercetin (Fig. 2) is classified as flavonoid compounds and generally presents as quercetin glycosides (Salehi *et al*., 2020). This compound has a keto carbonyl group in its molecule, and the oxygen atom on the first carbon is alkaline and can produce salts with strong acids. The molecular structure contains four active groups, i.e.,, the dihydroxyl group between ring A, *o*-dihydroxy group B, C ring C2, C3 double bond, and 4-carbonyl. The presence of phenolic hydroxyl groups and double bonds gives quercetin vigorous antioxidant activity (Yang *et al*., 2020). Quercetin effectively protects cell death induced by cisplatin, methotrexate, ciprofloxacin, NaF, $HgCl_2$, and cadmium (Diniz *et al*., 2020). The quercetin mechanism as a nephroprotective is reported to downregulate TNF-α, IL-1β, IL-6, and COX-2 by inhibiting MAPK and NF-κB pathways (Fig. 3). Also, quercetin can inhibit ROS formation in the kidneys (Liu *et al*., 2012). In addition, Rana *et al*. (2018) reported that Pb^{2+} competes with Ca^{2+} and interferes with calcium homeostasis resulting in the release of Ca^{2+} from stimulated mitochondria. This starts from the opening of the mitochondrial transition pore, resulting in total mitochondrial damage, generation of reactive species, and oxidative stress. Between cells, the proximal tubule is more susceptible to Pb-induced cellular damage, followed by apoptosis. Another study with proximal tubular cell culture from mice revealed that Pb^{2+} increases

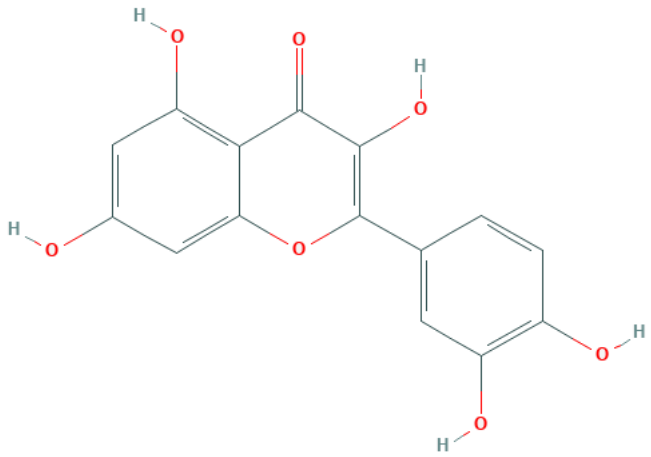

Figure 2. Quercetin structure (PubChem CID5280343).

cytosol and mitochondrial calcium concentration and depletes the ER by acting on inositol 1,4,5 receptor-triphosphate (IP3Rs) (Wang *et al*., 2015). Ca^{2+} involvement was also demonstrated by *in vitro* studies on HEK293 cells. This reveals that the potential for the transient canonical TRPC1 receptor actively participates in cytotoxicity and influx of Pb^{2+} (Zhang *et al*., 2014).

Another test related to the anti-inflammatory effect stated that quercetin could attenuate inflammatory mediators' production of IL-1β, IL-6, IL-8, and TNF-α LPS-induced HGF. The anti-inflammatory mechanism is through PPAR-γ activation, suppressing LPS-induced NF-κB activation (Xiong *et al*., 2019). Similar results revealed that quercetin was able to improve the LPS-induced inflammatory response in RAW264.7 macrophages significantly. This decreased inflammatory response through the inhibition of NF-κB, Erk1/2, and JNK signaling. The presence of hydroxy groups in flavonols has been confirmed to lead to a significant anti-inflammatory effect (Lee *et al*., 2018). Another result explained that quercetin has anti-inflammatory activity by inhibiting cytokine and nitric oxide synthase expression induced by inhibition of the NF-κB pathway without modifying the terminal-c-Jun N kinase activity (Comalada *et al*., 2005). The administration of quercetin and anticancer did not significantly affect the anticancer effects in an *in vivo* model using adenocarcinoma-induced mice. Proinflammatory TNF-α and intracellular mediators, such as activation of NF-κB p65 in renal tissue and iNOS expression, can be suppressed. The inhibition of renal cell apoptosis was also evaluated, where quercetin administration could suppress caspase-3 expression (Sanchez-Gonzalez *et al*., 2011). We conclude that there is a relationship between antioxidant and anti-inflammatory activity on the nephroprotective potency of flavonoid compounds, especially quercetin.

Combretum micranthum

In almost all West African regions, *C. micranthum* (CM) is usually grown wild and cultivated. This plant grows up to a height of up to 20 m or is a dense shrub (Welch *et al*., 2018). The leaves are used as herbal teas, trusted, and widely used in traditional medicine (Zahoui *et al*., 2017), including treating external wounds, malaria fever, coughs, and bronchitis (Olajide *et al*., 2003). The scientific results showed that CM has antimicrobial (Banfi *et al*., 2014; Martial *et al*., 2016; Udoh *et al*., 2012; Vroumsia *et al*., 2015), antityrosinase (Zeitoun *et al*., 2020), antihyperglycaemic (Chika & Bello, 2010; Welch *et al*., 2018), antihypertensive (Bourqui *et al*., 2020), antimalarial (Benoit *et al*., 1996), and anti-inflammatory activities (Olajide *et al*., 2003). CM aqueous extracts have more potent antioxidant activity than ethanol extracts (Touré *et al*., 2011). Recently, testing the antioxidant activity of hydroalcoholic extracts showed healthy antioxidant activity by scavenging AAPH, DPPH, nitric oxide, hydrogen peroxide, and chelating metal ions (Kpemissi *et al*., 2019).

CM nephroprotective activity has been demonstrated in *in vitro*, *in vivo*, and *in silico* experiments. In *in vitro* testing using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method using HEK-293 cells-induced cisplatin and CM (5, 10, 25, 50, 100, and 200 µg/ml), cell viability was significantly increased compared to the negative control. The EC_{50} value was 8.136 µg/ml. *In vivo* nephroprotective activity was evaluated by administering CM (200 and 400 mg/kg, per oral) to mice for 10 days, followed by a single intraperitoneal CP injection on the 5th day.

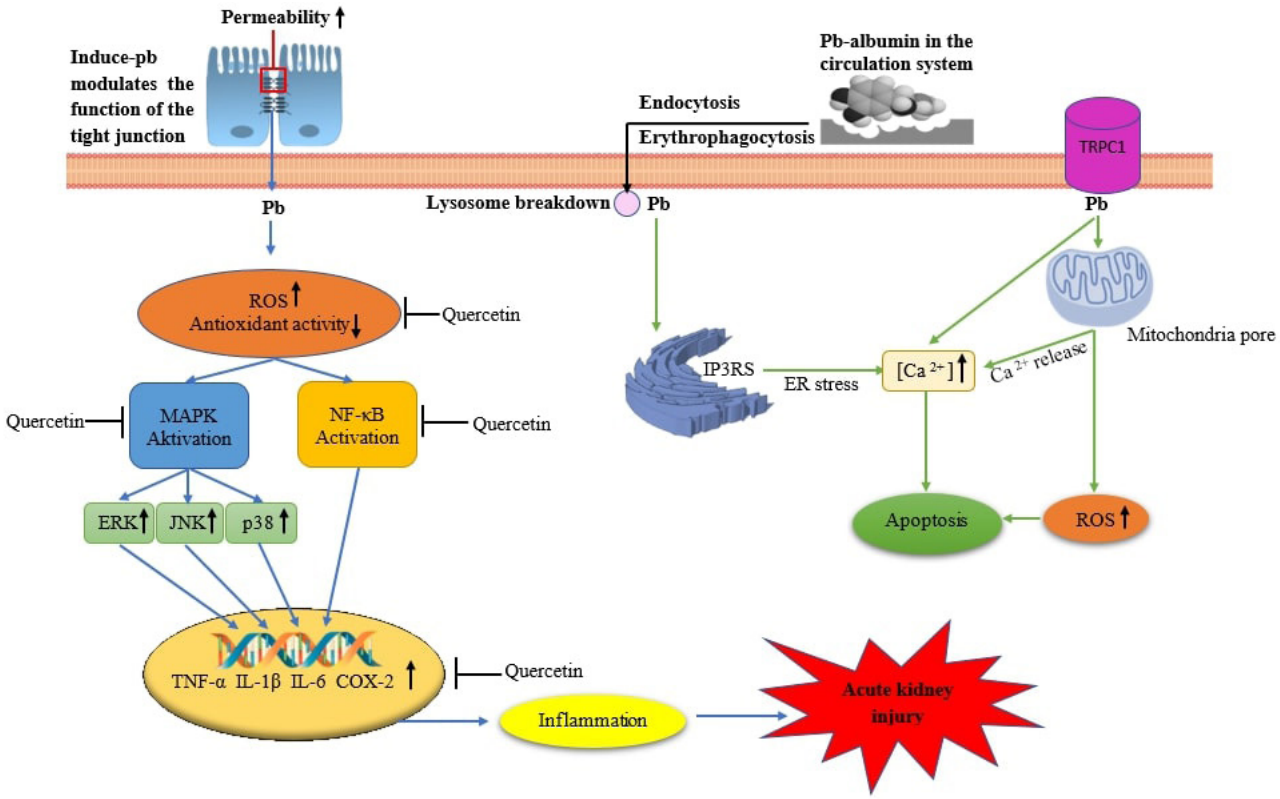

Figure 3. Schematic of the quercetin nephroprotective effect against various Pb-induced renal inflammation signals.

Administration of CM normalizes renal function at both doses by correcting markers of serum and urine renal damage, transaminases, markers of oxidative stress, and histopathological alteration in the kidneys. The *in silico* study showed that the docking score was higher in isovitexin and gallic acid against NF-κB and cianidanol and epicatechin against sEH (Kpemissi *et al*., 2019).

Homonoia riparia Lour.

Homonoia riparia is a shrub or small tree, grown near the riverbank and widespread from India to China, Laos, Philippines, Taiwan, and throughout Malaysia to Papua New Guinea (Pyun *et al*., 2017). Stems and leaves are used as laxatives, while infusions of wood are used to treat malaria and scabies. The leaves are used for skin infections in Malaysia and Thailand (Xavier *et al*., 2015; Zhai *et al*., 2012). Scientific evidence suggests that it has anticancer (Lee *et al*., 2012; Li & Wang, 2017), antimicrobial (Patil *et al*., 2014), antifungal (Bapat *et al*., 2012), antihyperuricemia (Xu *et al*., 2014), antiapoptosis (Pyun *et al*., 2017), anticoagulant (Kabbinale *et al*., 2015), and diuretic activities (Kumar *et al*., 2010).

Nephroprotective activity with *in vitro* experiments has been reported. Fractions of butanol and water from *H. riparia* (200 µg/ml) showed significant nephroprotective activity against cisplatin-induced cell damage in HEK-293 cells with the MTT test (Xavier *et al*., 2017).

Abelmoschus moschatus Medik., *Asparagus falcatus*, and *Barleria prionitis* Linn.

Abelmoschus moschatus is cultivated in the tropics of Asia, Africa, South America, and India. *A. moschatus* has various pharmacological activities, including diuretics, antioxidants, antiproliferative, antimicrobials, antilytic, hepatoprotective, memory strengthening, antidiabetic, hemagglutination, antiaging, antidepressants, anxiolytics, anticonvulsants, hypnotics, and muscle relaxants (Pawar & Vyawahare, 2017). In comparison, some *Asparagus* species are widely grown in Sri Lanka and used to treat chronic nephritis, stone urination, and diuretics (Napagoda *et al*., 2020). Furthermore, *B. prionitis* Linn., which is known as an ayurvedic herb, is widely grown in tropical Asia, Africa, and Yemen. Whole plants, ranging from leaves, stems, roots, and bark to flowers, have traditionally been used to treat toothache, cataract disease, whooping cough, inflammation, gland swelling, urinary tract infection, jaundice, fever, gastrointestinal disorder, tonics, and diuretics (Banerjee *et al*., 2012).

The three traditional Sri Lankan plants have been evaluated simultaneously for their *in vivo* nephroprotective activity in adriamycin-induced mice. The results showed water extracts at 200, 400, and 600 mg/kg, respectively; all three plants significantly decrease the serum creatinine, BUN, and total urine proteins, regardless of dosage. The highest nephroprotective activity indicated *B. prionitis* (Amarasiri *et al*., 2020).

Macrothelypteris oligophlebia (Bak.)

Macrothelypteris oligophlebia is distributed throughout southern China. This plant, one of the traditional Chinese herbs that have long been used to smoothen out blood circulation, removes blood stasis and dampness, edema, and inflammation (Yang *et al*., 2014).

Nephroprotective activity *in vivo* has been evaluated by a gentamicin-induction method in rats. The results revealed that

Table 1. The nephroprotective activity of medicinal plants.

Family	Plant	Part used	Solvent on test	Chemical constituents	Study	References
Combretaceae	*C. micranthum*	Leaf	Ethanol	Isovitexin, gallic acid, cianidanol, and epicatechin	*In vitro* *In vivo*	Kpemissi *et al*. (2019)
Euphorbiaceae	*Homonoia riparia* Lour.	All parts of the plant	Methanol, petroleum ether, ethyl acetate, butanol, and water	Gallic acid	*In vitro*	Xavier *et al*. (2017)
Malvaceae Lliliaceae acanthaceae	*A. moschatus* Medik. *A. falcatus* *B. prionitis* Linn.	Leaf	Water	Tannins, phenolics, flavonoids, steroid glycosides, terpenoids, and saponins	*In vivo*	Amarasiri *et al*. (2020)
Thelypteridaceae	*M. oligophlebia* (Bak.)	Rhizome	Ethanol	Matteucinol, naringenin, naringenin-4′-O-glucoside, protoapigenone, 5,7-dihydroxy-6,8-dimethyl flavanone, and protoapigenin-4′-O-β-d-glucoside	*In vivo*	Wu *et al*. (2012)
Solanaceae	*S. xanthocarpum*	Fruit	Petroleum ether and ethanol	Quercitrin and apigenin glycosides	*In vivo*	Hussain *et al*. (2012)
Asteraceae	*S. oleraceus*	Aerial	Ethanol	Sesquiterpene lactones, taraxasterol, luteolin, apigenin, caftaric acid, chicoric acid, villosol, ferulic acid, β-sitosterol, ursolic acid, rutin, and β-daucosterin	*In vivo*	Torres-González *et al*. (2018)
Bombacaceae	*C. pentandra* (L.) Gaertn.	Aerial	Methanol, dichloromethane, ethyl acetate, and *n* -butanol	Quercitrin, cinchonains 1a and 1b, cis -clovamide, trans -clovamide, and glochidioboside	*In vivo* and *in vitro*	Abouelela *et al*. (2020)
Simaroubaceae	*E. longifolia*	Root	Water	Data not available	*In vivo*	Chinnappan *et al*. (2019.)
Araliaceae	*D. morbifera*	Leaf	Methanol, n-hexane, chloroform, ethyl acetate, and n-butanol	Dendropanoxide and rutin	*In vivo* and *in vitro*	Kim *et al*. (2015)
		Leaf and stems	Water	neochlorogenic acid, syringin, chlorogenic acid, and rutin	*In vivo* and *in vitro*	Sachan *et al*. (2020)
Caricaceae	*C. papaya*	Leaf	Ethanol	Tocopherol, ascorbic acid, carpaine, deoxicempferol, kaempferol, deoxyquercetin, quercetin, dichumarol, coumaroylquinic acid, coumarin, folic acid, cystine, homocysteine, cysteine sulfoxide, l-glutamic acid, p-cumarellamic alcohol, dimethoxy phenol, umbilical alcohol caffeoyl, and methyl nonyl ketone	*In vivo*	Gheith and El-Mahmoudy (2018)
		Seed	Water	Saponins, tannins, flavonols, glycosides, terpenoids, alkaloids, reducing sugars, amino acids, fats, proteins, phenols, vitamins, sterols, and triterpenes	*In vivo*	Naggayi *et al*. (2015)
		Seed	Water	Data not available	*In vivo*	Kingsle (2012)
Zingiberaceae	*B. rotunda* (L.) Mansf.	Rhizome	Panduratin A isolated from the rhizome of *B. rotunda*	Panduratin A	*In vivo* and *in vitro*	Thongnuanjan *et al*. (2021)

extracts of *M. oligophlebia* at 250 and 500 mg/kg could inhibit the increased BUN and Cr levels. Additionally, activity was indicated by the influence on renal tissue enzymes, where there was a significant decrease in MDA and NO and an increase in SOD, CAT, and GSH-Px. The histopathological evaluation results showed that a dose of 500 mg/kg provides the best histological protection against the renal tubules' damage due to gentamicin induction (Wu *et al*., 2012).

Solanum xanthocarpum

Solanum xanthocarpum is a wild herbaceous plant widespread in many places in India (Singh and Singh, 2010). Traditionally, the boiled roots are used as antipyretic, diuretic, and expectorant. Seeds are efficacious as expectorants and asthma. Whole plants and fruits are used for bronchial asthma, thymitis, intestinal disorders, hemorrhoids, and dysuria (Parmar *et al*., 2010). Scientific evidence proves that *S. xanthocarpum* has anticancer

Table 2. *In silico* study: interaction between phytoconstituents and NF-κB.

Phytoconstituents	PDB ID NF-κB	Result	Reference
Curcumin	1NFK	*Curcumin* sulfate became the strongest inhibitor among all its derivatives in inhibiting the NF-κB p50 subunit with DG −8.94 kcal/mol, and KI predicted 0.24 lM.	Kumar and Bora (2012)
Gallic acid and palmitic acid	1SVC	Benzoic acid 3,4,5-trihydroxy (gallic acid) and ethyl ester hexadecanoic acid (palmitic acid) can inhibit NF-κB with GLIDE energy scores of −7.01477 and −7.72394 kcal/mol, respectively.	Muzaffer *et al*. (2017)
Quercetin and 1-caffeoylquinic acid	1SVC	Quercetin and 1-caffeoylquinic acid showed significant binding affinities of various phytochemicals with the Rel homology domain of the precursor protein NF-κB p105. Molecular inhibitors with bond energies of −12.11 and −11.50 kcal/mol, respectively.	Khan *et al*. (2013)
α-, β-, and γ-Mangosteen	4KIK	α-, β-, and γ-mangosteens can attenuate oxidative stress and inflammation that interacts with IP3R, KEAP-1, p38 kinase, JNK, and NF-κB. Docking scores against NF-κB of −7.187, −6.606, and −7.183, respectively. The predicted results suggest that xanthones have protective activity against oxidative stress and inflammation.	Rana *et al*. (2019)
Rutin, aviculin, quercetin, quercitrin, catechins, epicatechins, caffeine, and theobromine	Data not available	The docking of the nine active compounds *Scurrula atropurpurea*, where the compounds most easily bonded to the NFkB-IkB complex, respectively, are routine (−314.35 kJ/mol), aviculin (−311.75 kJ/mol), quercetin (−247.11 kJ/mol), quercitrin (−288.36 kJ/mol), catechins (−239.13 kJ/mol), kaempferol (−238.11 kJ/mol), epicatechin (−232.58 kJ/mol), caffeine (−170.13 kJ/mol), and theobromine (−162.28 kJ/mol).	Yuniwati *et al*. (2018)

(Bhutani *et al*., 2010; Kumar & Pandey, 2014), antioxidant (Ghassam *et al*., 2014; Kumar & Pandey, 2014; Kumar *et al*., 2012; Nithya *et al*., 2018; Priya *et al*., 2010), anthelmintic (Priya *et al*., 2010), antiurolithic (Patel *et al*., 2012), mosquitocidal (Kumar & Murugan, 2012), antibacterial (Amin *et al*., 2012; Nithya *et al*., 2018; Priya *et al*., 2010), hypoglycemic (Kar *et al*., 2006), anti-inflammatory (Anwikar & Bhitre, 2010; More *et al*., 2013; Ravi *et al*., 2009), and hepatoprotective activities (Hussain et al., 2012; Ghassam *et al*., 2014; Hussain *et al*., 2012; Singh *et al*., 2015).

An *in vivo* study showed nephroprotective activity using gentamicin-induced mice. Extracts of *S. xanthocarpum* at 200 and 400 mg/kg showed protection against increased renal weight ratio. At 400 mg/kg, it provides maximum protection against the index of kidney organs and increased urine output. Also, plasma and urine test results showed a significant decrease in urea and creatinine concentrations. Evaluation of kidney antioxidants was also conducted and proved that *S. xanthocarpum* can prevent the decreased activity of SOD, CAT, and GSH. Interestingly, 400 mg/kg showed maximum protection, almost the same as a standard control. Histopathological observations at 200 mg/kg showed slight degenerative and necrotic tubular alteration, compared to 400 mg/kg, indicating regeneration in tubular epithelial cells (Hussain *et al*., 2012).

Sonchus oleraceus

Sonchus species are annual herbaceous plants. A total of 50 species are widespread in Europe, Asia, and Africa (Li & Yang, 2018). In Chinese folk culture, this plant is commonly consumed by cooking and is believed to be a traditional medicine to treat inflammatory symptoms (Li *et al*., 2017). Pharmacological activities have been reported, including antiulcer (Saxena & Kumar, 2020), antiulcer and ulcerative colitis (El-meligy *et al*., 2018), antioxidant (Aissani *et al*., 2021; Mcdowell *et al*., 2011; Xia *et al*., 2011), anticancer (Huyan *et al*., 2016), hepatoprotective (Chen *et al*., 2020), analgesic (Cardoso *et al*., 2009), antidiabetic (Chen *et al*., 2019, 2020), anti-inflammatory (Chen *et al*., 2019; Li *et al*., 2017; Li *et al*., 2017; Vilela *et al*., 2010), antipyretic (Vilela *et al*., 2010), antidepressant (Vilela *et al*., 2010), antibacterial (Xia *et al*., 2011), antihemolytic (Dima *et al*., 2017), anticholinesterase (Aissani *et al*., 2021), open wound healing (Prichoa *et al*., 2011), and antiaging (Ou *et al*., 2015).

The nephroprotective activity was evaluated by the method of ischemia induction using renal pedicle occlusion for 45 minutes using a vascular brace. The clamp is pulled and reunited for 15 hours. The results showed that increased BUN, creatinine, MDA, SOD, TNF-α, IL-1β, and IL-6 were significantly weakened in mice given *S. oleraceus* extract at 300 mg/kg. A lower-scoring renal histopathological assessment showed minor damage than the group without *S. oleraceus* extract (Torres-González *et al*., 2018).

Ceiba pentandra (L.) Gaertn.

Ceiba pentandra is a Mexican native plant, widespread in Central America and the Caribbean, North and South America, and tropical West Africa (Van Dam & Gorshkova, 2003). This fast-growing tree species is known as "kapuk" (Gaertn *et al*., 2018). The bark decoction has been used as diuretic and aphrodisiac and to treat headaches and type II diabetes. It is used as an additive in several hallucinogenic beverages (Muhammad *et al*., 2016). *Ceiba pentandra* has the activity of antioxidant (Kiran *et al*., 2012, 2015; Loganayaki *et al*., 2013; Nguelefack *et al*., 2020), anti-inflammatory (Itou *et al*., 2014; Kiran & Rao, 2014), antidiarrhea (Njinga & Musa, 2009), hepatoprotective (Bairwa *et al*., 2010), antibacterial (Anosike *et al*., 2012; Khalir *et al*., 2020), anti-Alzheimer's (Abouelela *et al*., 2020), antidiabetic (Fofié *et al*., 2018; Nguelefack *et al*., 2020; Satyaprakash *et al*., 2013), and anticancer (Kumar *et al*., 2016).

Nephroprotective activity *in vivo* and *in vitro* has been reported. *In vivo* studies of MTX-induced nephrotoxic rats showed that the administration of ethyl acetate of *C. pentandra* at 400 mg/kg suppressed the increased serum creatinine, BUN, cystatin C, microalbuminuria, urine KIM-1, TNF-α, and CRP significantly. There was an increased SOD and CAT activity and GSH levels and a decreased renal MDA and NO levels. *In vitro* evaluation proved

that *C. pentandra* could significantly suppress the expression of mRNA proapoptosis caspase-3 and the expression of genes IL-18, TNF-α, and CRP. On the other hand, the expression of Bcl-2 antiapoptosis mRNA increases. The histopathological picture evaluation showed histological differences from the control group, except for renal vascular congestion in some areas observed (Abouelela *et al*., 2020).

Eurycoma longifolia

Eurycoma longifolia is a traditional herbal remedy. It is widespread in Indonesia, Malaysia, Vietnam, and Cambodia, Myanmar, Laos, and Thailand (Effendy *et al*., 2012). In Southeast Asia, this plant is known as "Tongkat Ali" (Bhat *et al*., 2010). This plant is used to treat sexual abnormalities, constipation, cancer, leukemia, recovery after illness, decreased libido, aging, stress, hypertension, malaria, osteoporosis, diabetes, fever, and gland swelling (Ezzat *et al*., 2019a). *Eurycoma longifolia* was reported to have antiosteoporosis (Chinnappan *et al*., 2020; Jayusman *et al*., 2018; Thu *et al*., 2018, 2019), aphrodisiac (Ezzat *et al*., 2019b; Tee *et al*., 2017), antihypertensive (Abdullah *et al*., 2004), antihyperuricemia (Bao *et al*., 2019), anticancer (Moses *et al*., 2021; Tung *et al*., 2017), and antidiabetic activities (Tsai *et al*., 2020).

The nephroprotective activity was evaluated with paracetamol-induced mouse models with *E. longifolia* extract at 100, 200, and 400 mg/kg. The results revealed that extracts at 200 and 400 mg/kg prevent a decreased total protein levels and albumin, close to normal. There are significantly decreased urea and creatinine levels with the same dose and an increase in dose-dependent creatinine clearance. The histopathological assessment showed that a 400 mg/kg dose provided the highest protection with a near-normal picture of the kidneys (Chinnappan *et al*., 2019).

Dendropanax morbifera

Dendropanax morbifera can be found throughout the southwestern regions of East Asia, Korea, Japan, the Malay Peninsula, and Central South America (Balakrishnan *et al*., 2020). Traditionally, it was used to treat infectious diseases, cancer, inflammation, diabetes, thrombosis, dermatopathy, and headaches (Choi *et al*., 2018). Scientifically, *D. morbifera* has been reported to have a variety of pharmacological activities, including anti-inflammatory (Birhanu *et al*., 2018; Choo *et al*., 2019), antioxidant (Bae *et al*., 2015; Shin et al., 2013), immunomodulator (Birhanu *et al*., 2018), neuroprotector (Kim *et al*., 2016, 2019), antihyperuricemia (Cho *et al*., 2018), anticancer (Wang *et al*., 2016), hepatoprotective (Bae *et al*., 2015; Eom *et al*., 2020; Yang *et al*., 2019), antiobesity, anticholesterol (Song *et al*., 2018), antiparkinson (Park *et al*., 2018), antimelanogenic (Lee *et al*., 2020; Park *et al*., 2020), and antihypertensive (Park *et al*., 2020).

The nephroprotective activity was evaluated *in vitro* and *in vivo*. In *in vitro* studies with MTT tests, the viability of cisplatin induction NRK-52E cells was assessed. Methanol extracts as well as subfractions each at a dose of 10 μM. Cell viability test showed that methanol and subfraction extracts ($CHCl_3$, EtOAc, *n*-BuOH, and H_2O fractions) protect cells against cisplatin-induced cytotoxicity, except the *n*-hexane fraction. $CHCl_3$ subfraction activity showed the most substantial protection among all subfractions. Also, the fraction inhibits the formation of ROS in NRK-52E cells and reduces damage to mitochondrial membranes. Mechanisms of improvement of ROS and activation of caspase-3 proapoptosis are also evaluated. The results prove that administration of subfractions of $CHCl_3$ can significantly reduce the activation of caspase-3, thus reducing cisplatin-induced renal tubule apoptosis. In *in vivo* studies, cisplatin-induced mice caused weight loss and increased index of renal organs and biochemical parameters of BUN and serum creatinine. The results proved that administration of subfractions of $CHCl_3$ weakens BUN and serum creatinine but does not affect relatively average body weight and kidney organ index (Kim *et al*., 2015)

Recently, nephroprotective activity was evaluated *in vitro* and *in vivo* with a renal fibrosis model in diabetic rats due to streptozotocin-induced. The results revealed that streptozotocin-induction could lose weight, increase kidney organs' index, and decrease microalbumin and Cr levels. Urine evaluation is carried out to validate the incidence of diabetic nephropathy with measurements of expression of KIM-1, NGAL, SBP1, and PKM2 and 3-IS in serum, kidney tissue, and urine. Evaluation of ROS production, antioxidant enzyme activity, and oxidative stress, proinflammatory cytokines, apoptosis, and ECM composition in the kidneys are also carried out. The results showed that administering *D. morbifera* extract at 25 mg/kg can restore kidney organs' index with relatively normal rat body weight growth during testing. Also, there was a decreased KIM-1, SBP1, PKM2, and NGAL in the urine, almost the same as in the standard group. Measurements of 3-IS concentrations in serum and kidney tissue show that the concentration of 3-IS in serum, kidney tissue, and urine decrease to resemble standard groups. Other results suggest that administration of *D. morbifera* extract may inhibit ROS production as well as increased GSH. The evaluation of oxidant enzyme activity showed increased activity of SOD and CAT and lower MDA levels. Also, proinflammatory cytokines (TGF-β1, IL-1β, and IL-6) can be suppressed, while IL-10 levels are increased. The evaluation results related to apoptosis showed that *D. morbifera* extract decreased the expression of cleaved-caspase-3 proteins and cleaved-caspase-9 and improved Bax expression. ECM evaluation showed that the expression of collagen-1, α-SMA, and fibronectin can be suppressed and decrease 4-hydroxyproline levels in renal tissue (Sachan *et al*., 2020).

Carica papaya

Carica papaya is a large herbaceous plant. It is found in almost all tropical regions of the Americas. This plant has become the most widely cultivated and consumed fruit in tropical and subtropical areas of the world, including India, Brazil, Mexico, Indonesia, Dominican Republic, Nigeria, and many other countries (Alara *et al*., 2020). It has been reported that traditionally this plant is used as an abortive drug, wound antiseptic, dyspepsia, venereal diseases, hemorrhoids, and framboesia. Fruit extracts and seeds have been reported to have bactericidal activity. The seeds have antiparasitic, sedative, muscle relaxant, antifertility, and laxative. The leaves have activity of hyperuricemia, hepatoprotective, hypoglycemia, and hypolipidemia activity (Adeneye, 2014).

The nephroprotective activity was evaluated *in vivo* using gentamicin-induced mice. Nephrotoxicity due to induction is shown to increase urea, creatinine, KIM-1, and clusterin in serum and urine and increase MDA production in kidney tissue. Besides, the picture of the damage is characterized by the infiltration of focal inflammatory cells between the tubules and the

surrounding blocked blood vessels, associated with the appearance of homogeneous eosinophilic casts in the denoted lumens of the tubules. Administration of extracts *C. papaya* of 150 and 300 mg/kg revealed that extract lowered urea, creatinine, KIM-1, and clusterin, which are almost equivalent to the control group, ascorbic acid. Besides, *C. papaya* extract decreased MDA production in kidney tissue and fixed most pathological alteration in focal inflammatory cellular infiltration among glomeruli and tubules in the cortex (Gheith and El-Mahmoudy, 2018). Other studies have also been reported with paracetamol-induced nephrotoxic models. The results suggest that extract at 500 and 750 mg/kg decreased creatinine, uric acid, and urea concentrations. A 750 mg/kg changes in the level of renal (Naggayi *et al*., 2015). Another study evaluation was carried out by CCl_4-induction, which affects electrolyte levels, where there were increased Na^+, Cl^-, urea, and creatinine levels, while there were decreased K^+ levels. Results showed that the administration of *C. papaya* extract led to significantly decreased Na^+, Cl^-, urea, and creatinine, but dose-dependent K^+ enhancement was insignificant (Nwangwa, 2012).

Boesenbergia rotunda (L.) Mansf.

Boesenbergia rotunda (local name temukunci) is a plant from the Zingiberaceae family, which has long been used traditionally, especially in Asia, to reduce stomach complaints, including flatulence and diarrhea, as an anti-inflammatory, and relieve inflammation caused by gum infections, wound healing, and cancer (Rosdianto *et al*., 2020). There are two major groups of phytoconstituents in this plant, including flavonoids and chalcone derivatives (alpinetin, cardamonin, pinostrombin, panduratin, pinocembrin, kaempferol, and quercetin) (Rosdianto *et al*., 2020). A series of studies have proven that this plant has various pharmacological activities, such as aphrodisiac (Ongwisespaiboon & Jiraungkoorskul, 2017), antibacterial (Bhamarapravati *et al*., 2006; Zainin *et al*., 2013), wound healing (Mahmood *et al*., 2010), antiglycation agent and inhibitor α-Glucosidase (Potipiranun *et al*., 2018), anti-inflammatory (Isa *et al*., 2012; Rosdianto *et al*., 2020), and cytotoxic (Break *et al*., 2021).

The nephroprotective effect of panduratin A isolated from *B. rotunda* has been reported by Thongnuanjan *et al*. (2021) in human renal proximal tubular cells (RPTEC/TERT1) and a model of AKI in cisplatin-induced mice. The results showed that panduratin A 20 mg/kg BW improved renal toxicity both *in vitro* and *in vivo* by inhibiting the activation of extracellular signal-regulated kinase (ERK)1/2 and caspase-3, thereby reducing apoptosis.

Molecular Interaction of Phytoconstituents with NF-κB: *In Silico* Study

NF-κB transcription factors regulate the innate and adaptive immune system and serve as an important mediator of inflammatory responses. NF-κB induces the expression of various proinflammatory genes, including those that encode cytokines and chemokines, and also plays an important role in inflammatory regulation. Another role of NF-κB is in regulating the survival, activation, and differentiation of innate immune cells and inflammatory T cells. As a result, the activation of modulated NF-κB contributes to the pathogenic processes of various inflammatory diseases (Liu *et al*., 2017). One of the most important strategies of the pathogenesis of AKI is through the systematic inhibition of the NF-κB approach, which can affect the condition of AKI (Song *et al*., 2019). *In silico* experiments have been conducted to rationalize the success or failure of certain interventions, in particular the regulation of NF-κB. This is the ultimate goal of the *in silico study*, which is to more efficiently track nonlinear inflammatory signals, thereby increasing understanding of how compounds interact to produce a response (Foteinou *et al*., 2009). Previous research has been conducted *in silico* to initiate the discovery of new medicinal compounds and to improve efficiency in optimizing the activity of parent compounds with a variety of different conditions but remain focused on NF-κB.

AKI is closely related to both intrarenal and systemic inflammatory responses. A better understanding of the cellular and molecular mechanisms underlying the inflammatory response is needed. This is the basis for further research related to the identification of effective therapies to prevent or improve AKI (Rabb *et al*., 2016). Activation of the NF-κB/Rel transcription family, by translocation of the nucleus of the cytoplasmic complex, plays a central role in inflammation through its ability to induce transcription of proinflammatory genes. These pathways are activated upon appropriate cellular stimulation, most often by signals associated with pathogens or stress (Tak & Firestein, 2001). The inflammatory response is a major highlight, and this is because of its role in the pathogenesis of AKI, where the regulation of NF-κB activity by the IκB and IKK proteins and the development of therapeutic strategies aimed at inhibiting NF-κB have always been of interest to study as the basis for the findings new drug candidate.

CONCLUSION

Many drugs when administered for a long period have been known for inducing AKI; however, the use of medicinal plants to prevent the damage is always interesting to be discussed, regardless of the pros and cons. Various types of plants that are often used traditionally as nephroprotective agents have been mentioned. All studies have been scientifically proven both *in silico* with the NF-κB regulatory approach as a signal for inflammation and *in vitro* and *in vivo* to protect the kidneys due to the induction of various nephrotoxic drugs. This review supports and confirms the usefulness of ethnomedicine, most of which have potential nephroprotective flavonoids. Most of the plants have nephroprotective-related antioxidant activity. Further research is recommended, regarding detailed efficacy and safety studies, especially on human subjects

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All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

CONFLICT OF INTEREST

There are no conflicts of interest related to the publication of this paper.

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