

Review Article

Nephroprotective activity of naringin against chemical-induced toxicity and renal ischemia/reperfusion injury: A review

Negin Amini^{1,2}, Maryam Maleki³, Mohammad Badavi^{1,2,*}

¹Department of Physiology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

²Persian Gulf Physiology Research Center, Medical Basic Sciences Research Institute, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

³Department of Physiology, School of Medicine, Ilam University of Medical Sciences, Ilam, Iran

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*** Corresponding Author:**

Tel: +98-6133367550-5

Fax: +98-2164112834

Badavi-m@ajums.ac.ir

badavim@yahoo.com

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Abstract

Objective: The kidney is well-known as the vital organ which is responsible for maintaining body homeostasis and secretion of toxic metabolites. Renal injury is accompanied by oxidative stress which results in cellular apoptosis, lipid peroxidation, and reduction of antioxidant levels. Plant extracts and their phytoconstituents, owing to free radical scavenging properties, seem to be valuable against modern synthetic and chemical drugs. Naringin is a flavonoid present in citrus fruits with pharmacologic effects including antioxidant, anti-inflammatory, and anti-apoptotic properties. This review summarizes the renoprotective effects of naringin and discusses mechanisms of its action against renal injury.

Materials and Methods: For this paper, original subject-related articles published up to October 2020 have been reviewed in the databases, including PubMed, Scopus, and Web of Science, and Google Scholar.

Results: Naringin increases antioxidant enzyme activity, and glutathione content, reduces lipid peroxidation and inhibits inflammatory cytokines. In the molecular investigation, naringin activates the *Nrf-2* signaling, prevents apoptosis signaling, and inhibits the autophagy pathway. Besides, naringin could protect the kidney through modulating *microRNA-10a* in the kidney tissue in an acute kidney injury model.

Conclusion: This review recommends that naringin can be considered a promising candidate to treat kidney dysfunction induced by oxidative stress in the future.

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Introduction

The kidney is a vital organ that is responsible for different functions in the body, such as the maintenance of body

homeostasis, as well as water and electrolyte balance, the exertion of toxic metabolites, and regulation of glomerular filtration (Bello-Reuss and Reuss, 1983;

Ferguson et al., 2008). In this regard, maintaining kidney health is essential, since kidney dysfunction leads to water-electrolyte imbalance, accumulation of metabolites, resulting in harmful consequences (Di Lullo et al., 2019). Environmental toxins, medicinal agents, and ischemia-reperfusion (I/R) have been demonstrated to cause acute kidney injury (AKI) (Abd Elmonem et al., 2018; Adil et al., 2015; Amini et al., 2019b). Oxidative stress is one of the main contributors to kidney injury that is associated with lipid peroxidation, depletion of antioxidant enzymes, cell apoptosis, mitochondrial dysfunction, and finally, cell death (Araujo and Welch, 2006; Ratliff et al., 2016).

Nowadays, preventive or supplementary medicine is applied to treat various chronic diseases (McDonough and Doucette, 2003) and plant-based dietary nutrients seem to be unique alternatives in the prevention and treatment of diseases, due to the side effects of chemical drugs and the lack of protective kidney medication in medicine (Martin and Appel, 2009; Yadav et al., 2020). It was confirmed that herbal-based nutrients, especially polyphenolic compounds (flavonoids, anthocyanins, and phenolic acids), possess potential health benefits (Kandemir et al., 2017; Martin and Appel, 2009). Flavonoids are the most potent antioxidants among polyphenolic compounds (Martin and Appel, 2009), which through antioxidant and inflammatory properties, can influence several molecular signaling pathways to protect organ function (Chen et al., 2018a; Chen et al., 2018b). *Citrus* plants are well-known as polyphenolic compounds, and naringin is one of the main flavonoids extracted from their fruits (Tripoli et al., 2007). Naringin ($C_{27}H_{32}O_{14}$, molecular weight: 580.4 g/mol) is a flavanone glycoside derived from naringenin (Zhang et al., 2014). It is found in grapes and citrus fruits and has a bitter taste of citrus juices (Chtourou et al., 2015). In the

intestine, gut microflora breaks down naringin to its aglycon, naringenin; then, it is absorbed through portal blood (Choudhury et al., 1999).

In experimental studies, it has been confirmed that following oral consumption and absorption through portal blood, naringin undergoes vast metabolisms which can control the bioavailability of naringin in the plasma. Naringin is eliminated via bile excretion by the liver (Alam et al., 2014; Tsai and Tsai, 2012). Oral acute and subchronic administrations of naringin indicate non-toxic effects in experimental studies (Li et al., 2013). In a rat model, it has been indicated that the median lethal dose (LD50) of naringin was 2000 mg/kg (Bo et al., 2013; Li et al., 2014). In numerous studies, antioxidant, anti-inflammatory, anti-apoptosis, metal chelating, and anti-carcinogenic properties of naringin have been proven (Camargo et al., 2012; Chtourou et al., 2016; Singh et al., 2004a). Considering several pharmacologic properties, high availability, and low cost, naringin could be considered a potential candidate for renal diseases.

The present review was done to determine the beneficial roles of naringin and its mechanisms of action in AKI (Naringin effects are summarized in Figure 1).

Materials and Methods

For this study, original subject-related articles published up to October 2020 have been reviewed in the databases, including PubMed, Scopus, and Web of Science, and Google Scholar. The search was performed using these keywords: “Naringin”, “kidney”, “nephrotoxicity”, “renal ischemia-reperfusion injury”, and “protective.” All articles that evaluated the effect of naringin on nephrotoxicity were included in this review (Table 1).

Naringin protect oxidative stress induced acute kidney injury

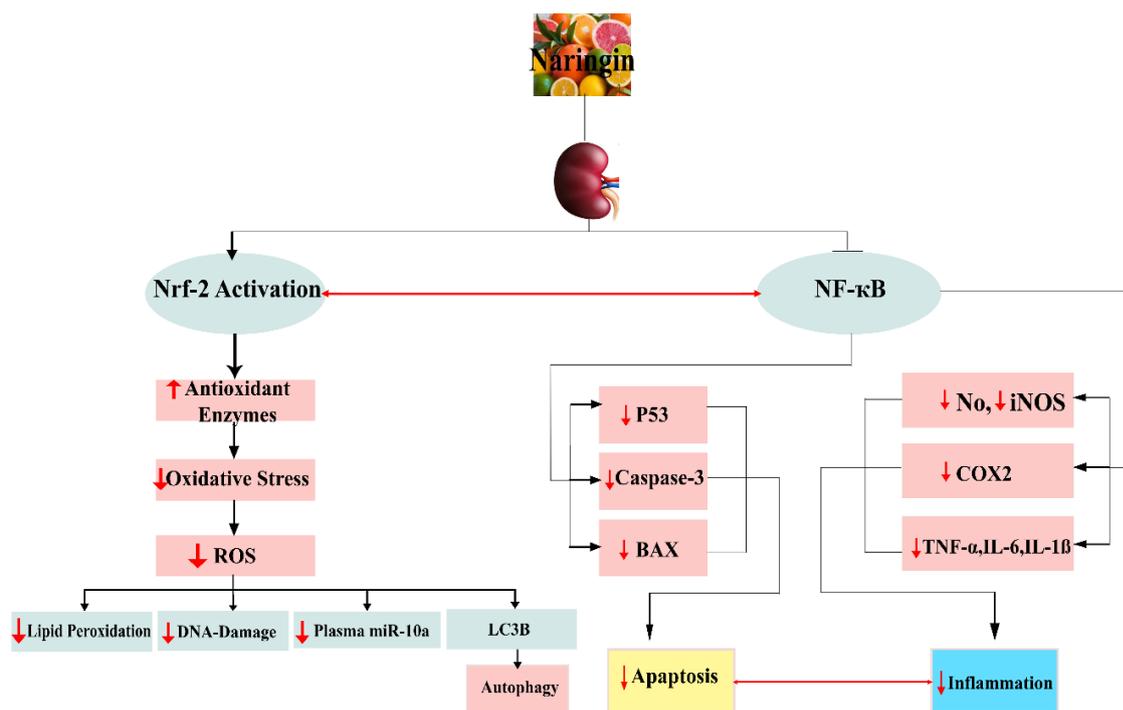


Figure 1. Naringin produces potential protective effect against AKI due to its antioxidative, anti-inflammatory, and antiapoptotic properties via upregulation of *Nrf-2* and downregulation of *miR-10a* and *NF-κβ*.

Results

The role of naringin in cisplatin nephrotoxicity

Cisplatin is one of the most common and potent chemotherapy drugs used for malignancy treatment (Pabla and Dong, 2008). The action mechanism of cisplatin for organ dysfunction is through oxidative stress (Pabla and Dong, 2008). Nowadays, the use of natural products is considered an alternative treatment (Martin and Appel, 2009). Elmoniem et al. showed that naringin improves kidney function by reducing malondialdehyde (MDA), tumor necrosis factor- α (TNF- α), cyclooxygenase-2 (COX-2), myeloperoxidase (MPO), and enhancing glutathione (GSH) (Taha et al., 2018). Chtourou and his colleagues have recommended that naringin exerts nephroprotective effects against cisplatin-induced toxicity by reducing blood urea nitrogen (BUN), creatinine (Cr), urea, uric acid, MDA, nuclear factor-kappa- β (NF- $\kappa\beta$), caspase-3, and reactive oxygen

species (ROS) levels, as well as by increasing GSH, catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GP_X), and glutathione transferase (GST) due to eliminating free radicals (Abd Elmonem et al., 2018; Chtourou et al., 2016).

The role of naringin in acetaminophen nephrotoxicity

Acute overdose or extreme chronic administration of acetaminophen (N-acetyl-p-aminophenol, APAP), leads to extreme side effects, including renal toxicity (Gum and Cho, 2013; Isik et al., 2006). APAP led to the metabolic activation of N-acetyl-p-benzoquinone imine (NAPQI). The overdose of APAP leads to a reduction in GSH content (Isik et al., 2006). Moreover, the overdose of APAP saturates the detoxication pathways of APAP due to sulfation insufficiency. Consequently, GSH depletion results in the accumulation of APAP, intensifying cellular oxidative stress (Jollow et al., 1973).

Table 1. Renoprotective effects of naringin against acute kidney injury

Study design (model), dose of Narginin (administration route, duration)	Model of AKI	Parameters	Results	References
<i>In vivo</i> (rat), 20, 40, and 80 mg/kg (orally, 14 days)	APAP, 700 mg/kg	SOD, GSH BUN, Cr, NO, MDA, KIM	Increase Decrease	Adill et al. (2016)
<i>In vivo</i> (rat) 20 mg/kg (orally, 4 weeks)	APAP, 0.5 gr/kg	GSH, GST, GPx, SOD Cr, Urea, Uric acid, MDA	Increase Decrease	Ahmed et al. (2019)
<i>In vivo</i> (rat), 80 mg/kg (orally, 7 days)	Cispaltin, 7 mg/kg	GSH MDA, Cr, Urea, COX-2, NO, MPO, TNF- α	Increase Decrease	Taha et al. (2018)
<i>In vivo</i> (rat), 25, 50, and 100 mg/kg (orally, 5 weeks)	Cispaltin, 5 mg/kg	The enzymes cascade, C _{cr} Lipide peroxidative markers, BUN, Cr, Uric acid, NO, TNF- α , p53, NF- κ B, iNOS, p53, Caspas-3	Increase Decrease	Chtourou et al. (2016)
<i>In vivo</i> (rat), 80 mg/kg (orally, 14 days)	Cispaltin 7 mg/kg	GSH Urea, Cr, MDA, COX-2, MPO, NO, TNF- α	Increase Decrease	Abd Elmonem et al. (2018)
<i>In vivo</i> (rat), 100, 200, and 400 mg/kg (orally, 60 min)	Glycerol, 8 ml/kg	GSH, CAT, SOD, GR, C _{cr} , C _{urea} BUN, Cr, MDA	Increase Decrease	Singh et al. (2004)
<i>In vivo</i> (rat), 100 mg/kg (IP, 14 days)	5-FU, 20 mg/mg	SOD, GSH BUN, Cr, TNF- α , IL-6, IL-1 α , Lipide peroxidative marker	Increase Decrease	Gelen et al. (2018)
<i>In vivo</i> (rat) 20,40, and 80 mg/kg (orally, 20 days)	Nickel, 20 mg/kg	The enzymes cascade, Urine output Lipide peroxidative markers, Urea, Cr, Nickel toxicity, Uric acid	Increase Decrease	Amudha and Pari (2011)
<i>In vivo</i> (rat), 20,40, and 80 mg/kg (orally, 28 days)	Sodium arsenite, 5 mg/kg	Urine Cr, SOD, GSH, Crc Cr, BUN, Uric acid, NO, MDA, KIM-1, TNF- α , Caspase-3, TGF- β	Increase Decrease	Adil et al. (2015)
<i>In vivo</i> (rat), 50 and 100 mg/kg (orally, 7 days)	Gentamicin, 120 mg/kg	GSH, GPx, GR, GST, SOD, CAT, and Vitamin C, NDH, SDH, COX Cr, BUN, Lipide peroxidative markers, TNF- α , IL-6, MPO, p53, NF- κ B, Caspase-3, Caspase-9, BAX	Increase Decrease	Sahu et al. (2014)
<i>In vivo</i> (rat), 50 and 100 mg/kg (orally, 7 days)	MTX, 20 mg/kg	SOD, GPx, CAT, GSH Urea, Cr, MDA, TNF- α , IL-1 β , IL-6, NF- κ β , iNOS, COX-2, Caspase-3, LC3B	Increase Decrease	Kandemir et al. (2017)
<i>In vivo</i> (rat), 40 mg/kg (orally, 21 days)	CsA, 25 mg/kg	The antioxidant cascade, HO-1 Lipide peroxidative markers	Increase Decrease	Chandramohan and Parameswari (2013)
<i>In vivo</i> (rat), 100, 200, and 400 mg/kg (Orally, 1 hr)	Fe-NTA, 8 mg/kg	CAT, GR, SOD, GSH BUN, Cr, MDA	Increase Decrease	Singh et al. (2004)
<i>In vivo</i> (rat), 50, and 100 mg/kg (orally, 7 days)	CYP, 200 mg/kg	SOD, GPx, CAT, GSH Urea, Cr, MDA, NF- κ β , TNF- α , IL-1 β , IL-6, iNOS, LC3B, Caspase-3, COX-2, 8-OHdG (marker of oxidative DNA damage)	Increase Decrease	Caglayan et al. (2018)
<i>In vivo</i> (rat), 400 mg/kg, (orally, 24 hr)	Renal I/R	C _{cr} , GSH, CAT, SOD BUN, Cr, MDA	Increase Decrease	Singh and Chopra (2004)
<i>In vivo</i> (rat), 100 mg/kg (IP, 7 days)	Renal I/R	C _{cr} , RBF, SOD, GPx, BCL-2 BUN, Cr, FE _{Na} , miR-10a, BAX, Caspase-3	Increase Decrease	Amini et al. (2019)
<i>In vivo</i> (rat), 100 mg/kg (IP, 7 days)	Renal I/R	CAT, TAC, Nrf-2 MDA	Increase Decrease	Amini et al. (2019)
<i>In vivo</i> (rat), 25,50, and 100 mg/kg (orally, 28 days)	STZ, 40 mg/kg	PPARY, HSP-72, SOD, GSH NF- κ B, TBARS	Increase Decrease	Sharma et al. (2011)
<i>In vivo</i> (rat), 20,40, and 80 mg/kg (IV, 12 weeks)	STZ, 60 mg/kg HG-induced podocytes	SOD, GSH-Px BUN, Cr, Urinary Protein, MDA, ROS, Caspase-3, NOX4	Increase Decrease	Zhang et al. (2017)

BUN: Blood urea nitrogen; Cr: Creatinine; KIM-1: Kidney injury molecule-1; GSH: Glutathione; GST: Glutathione transferase; GPx: Glutathione peroxidase; SOD: Superoxide dismutase; MDA: Malondialdehyde; TBARS: Thiobarbituric acid reactive substances; COX-2: Cyclooxygenase-2; NO: Nitric oxide; MPO: Myeloperoxidase; TNF- α : Tumor necrosis factor- α ; NF- κ B: Nuclear factor-kappa-B; GR: Glutathione reductase; IL-6: Interleukin-1 α ; IL-1 α : Interleukin-1 α ; CAT: Catalase; BAX: Bcl-2 associated x protein; BCL-2: B-cell lymphoma 2; RBF: Renal blood flow; miR-10a: MicroRNA-10a; Nrf-2: Nuclear factor erythroid 2-related factor 2; LC3B: light chain 3B; HO-1: Heme oxygenase1; TGF- β : Transforming growth factor beta; ROS: Reactive oxygen species; NDH: NADH dehydrogenase; SDH: Succinate dehydrogenase; FE_{Na}: Fractional excretion of sodium; PPAR γ : Peroxisome proliferator-activated receptor-gamma; HSP-72: Heat-shock proteins; NOX4: NADPH oxidase; 5-FU: 5-fluorouracil; APAP: N-acetyl-p-aminophenol; MTX: Methotrexate; CsA: Cyclosporine; Fe-NTA: Ferric nitrilotriacetic acid; CYP: Cyclophosphamide; I/R: Ischemia/reperfusion; STZ: Streptozotocin

Naringin protect oxidative stress induced acute kidney injury

Naringin inhibited oxidative stress induced by APAP by decreasing MDA and augmenting antioxidant enzymes, including SOD, GP_x, GST, and GSH content in the kidney tissue. Likewise, naringin pretreatment ameliorated plasma BUN and Cr levels, indicating improved kidney function (Adil et al., 2016; Ahmed et al., 2019).

Histopathological changes, including glomerular hypertrophy, congestion of renal vessel, pyknosis, and karyorrhexis, as well as markers of inflammation were appeared in APAP-induced kidney toxicity in rats, indicating renal cell death, which was relieved via an antioxidant effect of naringin (Adil et al., 2016; Ahmed et al., 2019).

Kidney injury molecule-1 (KIM-1) is considered as a new prognostic biomarker, which plays a pivotal role in the manifestation of renal injury (Ichimura et al., 2008; Visnagri et al., 2015). Oxidative stress induced by APAP elevated *KIM-1* expression in kidney tissue, whereas naringin administration modified enhancement of renal *KIM-1* expression in APAP-exposed rats (Adil et al., 2016). Taken together, these findings recommended that the beneficial effects of naringin might be mediated, at least in part through increasing the antioxidant defense system and suppressing oxidative stress.

The role of naringin in cyclophosphamide nephrotoxicity

Cyclophosphamide (CYP) is an anti-neoplastic medicine which is extensively used for the treatment of numerous diseases (Sinanoglu et al., 2012). Histopathology alterations in the kidney, depletion of GSH, and enhanced renal MDA level are caused by CYP (Sugumar et al., 2007).

An experimental study reported that CYP activated inflammatory, apoptotic, and autophagic pathways. CYP leads to reduced antioxidant capacity, including GSH, and enhances lipid peroxidation, which produces oxidative stress; the lack

of GSH content has been ascribed to the direct conjugation of CYP and its metabolites with an SH- group (Rehman et al., 2012). According to an experimental study, naringin recovered the levels of non-enzymatic (GSH) and enzymatic antioxidants (SOD, GP_x, and CAT). In addition, CYP-induced inflammatory responses were decreased, indicating the renoprotective effect of naringin due to removing free radical oxygen. Moreover, the administration of naringin considerably decreased the expression of 8-OHdG which is identified as an index of oxidative DNA damage. Also, CYP-induced the apoptotic and autophagic pathways by enhancing *caspase-3* expression and *light chain 3B (LC3B)* level, indicating that naringin protects CYP-induced nephrotoxicity through suppressed apoptotic and autophagy pathways (Rehman et al., 2012).

The role of naringin in 5-fluorouracil nephrotoxicity

5-fluorouracil (5-FU) is categorized as an anti-metabolic agent which is generally used for the treatment of multiple cancers (Longley et al., 2003). 5-FU leads to overproduction of ROS like the other chemotherapeutic agents and causes harmful outcomes and toxicity in kidney and liver tissues (Gelen et al., 2018; Longley et al., 2003). Depletion of antioxidant capacity elevated MDA content, and kidney dysfunction was reported in rats exposed to 5-FU (Gelen et al., 2018).

Administration of naringin significantly attenuated 5-FU-induced oxidative stress by modulating cellular antioxidant capacity. Naringin pretreatment recovered SOD and GSH, resulting in a considerable reduction in kidney MDA levels and improvement of kidney function. Moreover, inflammatory mediators' levels, including interleukin-1 α (IL-1 α), TNF- α , and interleukin-6 (IL-6) were inhibited with naringin treatment, which confirms the anti-inflammatory effect of naringin

following 5-FU nephrotoxicity (Gelen et al., 2018).

The role of naringin in methotrexate nephrotoxicity

Methotrexate (MTX) has been used to treat multiple cancers, but due to numerous side effects such as nephrotoxicity, its usage has been limited in clinics (Kalemci et al., 2015). Like the other chemotherapeutic drugs, not only MTX depletes the antioxidant enzyme systems but it also could produce ROS (Kandemir et al., 2017). Among the different agents that have diminished the anticancer drug-induced oxidative stress, natural products have been received substantial interest, owing to their uniqueness (Benzer et al., 2012; Gülcin, 2012). Cytosolic nicotinamide adenosine diphosphate (NADP)-dependent dehydrogenases and NADP malic enzymes are suppressed by MTX to decline the amount of NADPH in the cells (Abdel-Raheem and Khedr, 2014). In physiologic situations, NADPH converts glutathione into reduced glutathione which is essentially a non-enzymatic antioxidant to protect cells against oxidative damage (Bubici et al., 2006). MTX-induced renal toxicity reduces the cellular defense system via diminishing GSH content and antioxidant enzyme levels, which result in cellular damage by changing macromolecular structures including membrane lipids, proteins, and nucleic acids. Thus, the enhancement of lipid peroxidation can occur (Kandemir et al., 2017). Caspase is the main effector in apoptotic cell death, and caspase-3 has an essential function in activating cell death signals among caspases (Jänicke et al., 1998). MTX provoked apoptosis and autophagy via increasing *caspase-3* and *LC3B* levels (Kandemir et al., 2017).

NF- κ B is activated by oxidative stress situations, resulting in the generation of inflammatory mediators by MTX (Kandemir et al., 2017). Naringin administration was able to increase GSH

content and antioxidant enzymes, which was accompanied by lipid peroxidation inhibition in the kidney tissue. Additionally, naringin reduced *LC3B* and *caspase-3* levels that indicate a renoprotective effect of naringin through anti-autophagic and anti-apoptotic properties in MTX nephrotoxicity (Kandemir et al., 2017).

The role of naringin in cyclosporine (A) nephrotoxicity

Cyclosporine (CSA) is considered an immunosuppressant drug to prevent the rejection of organs in transplantation (Busauschina et al., 2004). ROS have been shown as detrimental agents in various renal injuries, including nephrotoxicity (Anjaneyulu et al., 2003). CSA-induced oxidative stress results in structural kidney damage and a reduction of glomerular filtration rate (GFR) confirmed by histopathological findings (Chandramohan and Parameswari, 2013). Nowadays, many researchers have been attracted to citrus flavonoids owing to their beneficial role in health (Anjaneyulu et al., 2003). Naringin has been able to enhance the renal enzyme and non-enzymatic antioxidant levels and reduce lipid peroxidation. The detailed mechanism of ameliorating CSA-induced nephrotoxicity by naringin, is unknown (Chandramohan and Parameswari, 2013).

The heme oxygenase (HO) enzyme system has two significant isoforms: HO-1 and HO-2. HO-1 induction has beneficial effects in diseases, and its protective properties are manifested by its anti-inflammatory, anti-apoptotic, and antioxidant effects (Nath, 2006). The mRNA and protein level of *HO-1*, which catalyzes the rate-limiting part of heme degradation, markedly reduced following treatment with CSA in rats (Chandramohan and Parameswari, 2013).

In the molecular investigation, naringin administration caused a significant elevation of mRNA and protein levels of *HO-1* in renal tissue, implying cytoprotective effects of naringin in a

CSA-induced toxicity model (Chandramohan and Parameswari, 2013).

The role of naringin in gentamycin nephrotoxicity

Gentamicin (GM) is identified as one of the most common aminoglycoside antibiotics. Owing to the low cost, low-level resistance, and easy availability, it is administered for the treatment of infections resulting from Gram-negative aerobes (Ali et al., 2011; Negrette-Guzmán et al., 2013). Despite its salutary effects, profound implications like nephrotoxicity are the limiting factors for using aminoglycosides (Sun et al., 2013). Experimental studies recommend that ROS play a role in lipid peroxidation and reduced enzymatic antioxidant system in the nephrotoxicity model including GM-induced nephrotoxicity (Balakumar et al., 2010; Lee et al., 2012). GM-induced ROS generation is an important key to cause ROS mitochondrial production and subsequently, mitochondrial dysfunction, which triggers apoptosis signaling (Morales et al., 2010; Juan et al., 2007; Bae et al., 2014).

Recently, naringin received considerable attention in treating various diseases as a free radical scavenger (Tripoli et al., 2007). GM-induced nephrotoxicity results in ROS overproduction that damages protein molecules and degrades the membrane-bound phospholipids, leading to lipid peroxidation, while naringin treatment changed this enhanced lipid peroxidation (Sahu et al., 2014).

Antioxidant enzymes SOD, CAT, GPx, GR (glutathione reductase), and GST activities, and non-enzymatic antioxidant levels (GSH and vitamin C) were remarkably decreased in GM nephrotoxicity. A reduction of GSH content is due to overproduction of GM-induced free radicals, or increased use of GSH to protect proteins containing -SH group against free radicals (Sahu et al., 2014).

Furthermore, the extensive formation of free radicals contributes to reducing SOD and CAT activities in GM-induced nephrotoxicity. However, naringin administration improved antioxidant enzyme activity. These observations confirm the hypothesis that the beneficial effects of naringin are related to enhancing the antioxidant defense system (Sahu et al., 2014).

Mitochondrial dysfunction is considered one of the mechanisms of GM-induced nephrotoxicity; in fact, ROS overproduction leads to kidney morphological and functional changes (Sahu et al., 2014). Administration of naringin ameliorated mitochondrial function, showing enhancement of the activities of mitochondrial respiratory enzymes (Sahu et al., 2014). Mitochondrial membrane permeability, associated with GM nephrotoxicity, results in the activation of apoptosis signaling (Sahu et al., 2014).

However, naringin administration reduced the level of *cleaved caspase-3*, *Bcl-2 associated x protein (Bax)*, and *p53* protein expression and promoted the *B-cell lymphoma 2 (Bcl-2)* protein level (Sahu et al., 2014). Thus, naringin could affect intrinsic/extrinsic apoptotic signaling pathway through inhibition of *p53*, *Bax*, and elevation of *Bcl-2* expression in the renal tissue of GM-administered rats.

Other findings indicated that the enhanced oxidative stress was reduced by naringin, which could be owing to naringin antioxidant, anti-inflammatory, anti-apoptosis, and mitochondrial protection properties (Sahu et al., 2014).

The role of naringin in ferric nitrilotriacetate nephrotoxicity

Ferric nitrilotriacetic acid (Fe-NTA) is an iron chelating that leads to a significant enhancement of lipid peroxidation and renal oxidative injury, ultimately inducing proximal tubular necrosis (Singh et al., 2004a). Fe-NTA induced a remarkable kidney oxidative stress indicated by

increased MDA and reduced renal CAT, SOD, and GR levels (Singh et al., 2004a).

An experimental study reported that pretreatment with a single dose of naringin decreased levels of BUN and Cr in Fe-NTA nephrotoxicity. Naringin pretreatment significantly ameliorated kidney dysfunction and morphological alterations, diminished MDA, and recovered the depleted renal antioxidant enzymes (Singh et al., 2004a).

The role of naringin in glycerol-induced nephrotoxicity

AKI induced by glycerol is associated with tremendous oxidative stress which results in kidney vasoconstriction, direct cytotoxicity, and cast formation. Administration of naringin amended lipid peroxidation and increased the level of antioxidant enzymes and GSH in the kidney in glycerol-treated rats (Singh et al., 2004b). Naringin possesses the potential antioxidant properties which recover kidney dysfunction, thereby increasing the antioxidant capacity and decreasing lipid peroxidation in the tissue (Singh et al., 2004b).

The role of naringin in heavy metal nephrotoxicity

Pollution caused by heavy metals is the most common micro-element pollutants in the environment. Toxic metals, including arsenic, cadmium, lead, and nickel, through overproduction of ROS, contribute to disturbing antioxidant system balance which ultimately leads to the undesirable effects on human health (Adil et al., 2015; Amudha and Pari, 2011; Nejabat et al., 2017).

The role of naringin in nickel nephrotoxicity

Nickel is well-known as an environmental pollutant that is used in industry. Cigarette smoking and ingesting contaminated foodstuffs cause the transportation of nickel to various organs, including the kidney that leads to renal cell

injury (De Brouwere et al., 2012; Edelman and Roggli, 1989; Gitlitz et al., 1975). Nickel toxicity is associated with oxidative stress, alterations of histopathology, a significant increase of plasma BUN and Cr levels, and reduction of Cr clearance (Amudha and Pari, 2011).

The effects of naringin in nickel-induced renal toxicity have been reported by Amudha and Pari (Amudha and Pari, 2011). Administration of naringin led to ameliorating kidney function and reducing lipid and protein peroxidation indexes, indicating the free radical scavenging properties (Amudha and Pari, 2011). Moreover, a significant decrease in nickel accumulation in the kidney tissue was reported following naringin treatment, showing that the hydroxyl groups of naringin could bind to nickel, raise the excretion of nickel and prevent the accumulation of nickel in kidney tissues; so, naringin decreases toxic effects of nickel (Amudha and Pari, 2011).

The role of naringin in arsenic nephrotoxicity

Arsenic is well-known as a toxic agent in the environment, causing harmful effects in organs of animals and humans (Kimura et al., 2006; Liu et al., 2000; Singh and DuMond, 2007). Oxidative stress, inflammatory factors, and apoptosis pathways are mechanisms for arsenic toxicity (Adil et al., 2015).

The beneficial effects of naringin on sodium arsenite-nephrotoxicity were investigated by Adil et al. (2015). Pretreatment with naringin remarkably enhanced SOD enzyme activity and GSH content, decreased MDA level in the kidney, and reduced plasma BUN and Cr levels (Adil et al., 2015). At the molecular level, naringin could suppress the increase of inflammatory cytokine *TNF- α* , *caspase-3*, and *KIM-1* in the kidney. The result of this study showed oxidonitrosative stress in renal tissue was recovered by naringin through its antioxidant, anti-apoptosis, and

anti-inflammatory properties (Adil et al., 2015).

The role of naringin in streptozotocin nephrotoxicity

It has been estimated that almost half the diabetic individuals have type 2 diabetes mellitus (T2DM), with the most common complications of diabetic nephropathy (DN) (Shaw et al., 2010; Wang et al., 2011). Growing evidence demonstrated that oxidative stress is considered a critical agent in the exacerbation of pathogenesis of DN (Wolf and Ziyadeh, 2007).

Streptozotocin (STZ) has been commonly utilized to create experimental models of diabetes through its cytotoxic action on pancreatic β -cells (Rodríguez et al., 2018). STZ's toxic effect is associated with oxidative damage, inflammation, and apoptosis (Sharma et al., 2011).

Numerous studies have shown that the administration of naringin remarkably ameliorates antioxidant status in diabetic rats (Sharma et al., 2011; Zhang et al., 2017). Naringin significantly improved the altered levels of antioxidant enzymes (SOD and GP_x) and reduced lipid peroxidation biomarkers in the kidney tissue and serum. The contents of MDA, and pro-inflammatory cytokines IL-6 and TNF- α in both serum and kidney were diminished following naringin administration in diabetic rats, indicating the inhibition of lipid peroxidation generation, inactivation of NF-KB, and suppression of free radical production (Sharma et al., 2011; Zhang et al., 2017). An *in vitro* study suggests that naringin inhibits ROS generation and reduces the MDA level in high glucose-treated podocytes (Zhang et al., 2017). Naringin prevented the NF-KB overexpression induced by oxidative stress in STZ rats by removing ROS, which activated this molecular pathway (Sharma et al., 2011). PPAR γ (peroxisome proliferator-activated receptor-gamma) is identified as a nuclear receptor that applies its action through

anti-inflammatory, and antioxidant effects in glomeruli (Michalik and Wahli, 2006). Additionally, heat-shock proteins (HSP) protect cells against many stressors by potential antioxidant and anti-inflammatory effects (Chung et al., 2008). Investigation of molecular has revealed that naringin results in PPAR γ , HSP-27, and HSP-72 overexpression in STZ-induced DN in rats (Sharma et al., 2011). Besides, NADPH oxidase 4 (NOX4) as the primary source of ROS production in renal cells, was downregulated by naringin in DN rats (Zhang et al., 2017). Following ROS production, the activation of caspase-3 as a key for the execution of apoptosis signaling occurs, which was repressed in the presence of naringin in STZ-induced DN in rats and HG-treated podocytes (Zhang et al., 2017).

Microscopic study of kidney tissue from STZ rats manifested hydropic changes in proximal convoluted tubules and widening of the matrix, which were improved by naringin (Sharma et al., 2011).

To sum up, it can be recommended that the protective effects of naringin is attributed to antioxidant properties. Moreover, naringin improved renal dysfunction which occurred by upregulation of PPAR γ , HSP-72, and HSP-27, suppression of NF-k β , and anti-apoptosis effect.

The role of naringin in renal I/R injury

Renal I/R injury is identified as one of the most common causes of AKI (Shoskes and Halloran, 1996). During ischemia, regeneration of ROS, alteration of cell membrane permeability, and imbalance of ions occur. Although reperfusion is essential for providing ATP production, it intensifies tissue injury through ROS overproduction and apoptosis (Kalogeris et al., 2012).

Recently, the role of naringin by free radical removal has been noted in health (Kalogeris et al., 2012). The salutary effects of naringin in renal I/R injury

models have been documented (Ammini et al., 2019b). Naringin pretreatment remarkably recovered the levels of antioxidant and suppressed MDA level in the kidney tissue in a renal I/R model (Ammini et al., 2019a; b). Moreover, an experimental study reported that naringin changed BUN and Cr levels in the plasma that demonstrated improvement of kidney function (Ammini et al., 2019b).

Moreover, molecular analysis showed that naringin significantly down-regulated *caspase-3* and *Bax* mRNA and augmented the Bcl-2 expression level (Ammini et al., 2019b). Nuclear factor erythroid 2-related factor 2 (*Nrf-2*) is identified as a cell-protecting agent against stressors including ROS, and radiation that regulate the transcription of antioxidant enzyme genes (Huang et al., 2015). Naringin administration increased kidney *Nrf-2* mRNA expression in renal I/R injury, indicating cell protection due to induction of the transcription of critical antioxidant enzyme genes (Ammini et al., 2019a).

MicroRNA-10a (*miR-10a*) is identified as a kidney tissue-specific microRNA, released from the tissue into the plasma following oxidative stress (Wang et al., 2012). Naringin caused a reduction in the renal I/R-induced high plasma *miR-10a* level that suggests its cytoprotective effect. These findings exhibited that naringin, in optimal concentration, exerts renoprotective effects through upregulation of *Nrf-2*, which is associated with increasing activity of antioxidant enzymes, reducing apoptosis, and downregulation of *miR-10a* level in a renal I/R injury model (Ammini et al., 2019a; b).

Discussion

According to the mentioned points, AKI is associated with a group of markers such as elevated BUN and Cr and inflammation responses to renal failure. Nowadays, herbal medicines, due to less side effects, are used instead of chemical medicines. In this regard, naringin which

has anti-inflammatory and potential free radical scavenging effects inhibits glomerular dysfunction and renal injury. Naringin can prevent kidney injury through various pathways. Naringin has limited the oxidative stress by triggering the *Nrf-2* pathway and declined pro-inflammatory factors such as *COX-2*, *TNF- α* , *iNOS*, and apoptosis agents. Natural products could stimulate the *Nrf-2* signaling pathway to regulate the gene expression of antioxidants (Molaei et al., 2021). This review promises the potential clinical applications of naringin, after undergoing clinical trials, in the treatment and prevention of kidney disease.

Conflicts of interest

The authors have declared that there is no conflict of interest.

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