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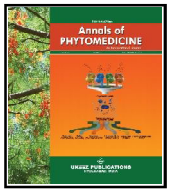

Review Article : Open Access

Therapeutic potential of quercetin for the prevention of various drug and chemical-induced nephrotoxicity: A review

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Abstract

Quercetin is a flavonoid and has been reported to have a wide range of pharmacological properties. The possible mechanisms involved in the nephroprotective activity of quercetin were discussed in this review. Quercetin exhibited nephroprotective activity against valproic acid, cisplatin, doxorubicin, streptozotocin, sodium fluoride, methotrexate, lead acetate, cadmium, lindane, adenine, paracetamol, gallium arsenide, chlorpyrifos, TiO_2, ferric nitrile triacetate, dichlorvas, melphalan, $HgCl_2$, ischaemic reperfusion, gentamicin, snake venom, ammonium fluoride, arsenate, atrazine, Ionising radiation and iron in various animal models due to its antioxidant, free radical-scavenging, anti-inflammatory, anti-apoptotic mechanisms. In this review, we provide an overview of the possible mechanisms by which quercetin reduced the nephrotoxicity-induced by different nephrotoxicants. This will help the scientific community to reduce the nephrotoxicity using quercetin.

1. Introduction

Flavonoids are a group of antioxidants affecting basic cell function such as growth, differentiation and apoptosis, because of their radical scavenging activity (Ilic *et al.*, 2014). Quercetin (QR) is a 3, 5, 7, 3, 4-pentahydroxyflavon, having the five hydroxyl groups placed at five different positions (Muhammad *et al.*, 2018). It has a bitter flavor and is widely distributed in fruits and vegetables. Buckwheat tea has a large amount of QR. QR is widely used in research and clinical trials. It has been proved to be having effective free radical scavenging activity, thus acts as an antioxidant (Ferry *et al.*, 1996). In addition, it also possesses anti-inflammatory, anti-apoptotic, hepatoprotective (Manoj *et al.*, 2021), renoprotective, neuroprotective (Paramita *et al.*, 2021) and cardioprotective effects (Chandrasinh *et al.*, 2021; Pingili *et al.*, 2020).

QR is now largely utilized as nutraceutical and as a phytochemical medication for different diseases. Owing to its basic chemical structure, the most obvious feature of QR is its strong antioxidant activity (Harshad *et al.*, 2020) which may potentially enable it to quench free radicals from forming resonance stabilized phenoxyl radicals (Veerendra *et al.*, 2021; Miltonprabu *et al.*, 2017). In this review, the nephroprotective effects of QR against drugs and various toxic agents have been discussed (Table 1).

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2. Nephroprotective activity of quercetin

2.1 Protective activity against valproic acid (VPA)-induced nephrotoxicity

VPA is used in treatment of epilepsy for various kinds of seizures. It induces release of free radicals and thereby causes lipid peroxidation and subsequent nephrotoxicity (Figure 1A). A study has shown that QR (0.05 mM) has nephroprotective activity against VPA-induced nephrotoxicity (20 mg/kg) by inhibiting lipid peroxidation using an *in vitro* model (Chaudhary *et al.*, 2015).

2.2 Protective activity against cisplatin (CS)-induced nephrotoxicity

CS is an antitumoral drug used for treatment of various types of cancers. CS induces mitochondrial injury and stimulates production of ROS and triggers inflammatory responses resulting in nephrotoxicity (Figure 1B). A study has demonstrated that QR (50 mg/kg/day, IP) prevented the nephrotoxic effect of CS (4 mg/kg, IP)

without affecting its antitumour activity by inhibiting the production of ROS using an *in vivo* model (Sanchez-Gonzalez *et al*., 2011).

2.3 Protective activity against doxorubicin (DOX)-induced nephrotoxicity

DOX is an agent used to cure various cancers. DOX causes oxidative damage and induces lipid peroxidation and apoptosis of mesangial cells and epithelial cells resulting in nephrotoxicity (Figure 1C). A study has demonstrated that QR (10, 50, and 100 mg/kg, PO) protected against DOX-induced nephrotoxicity (15 mg/kg, IP) with a provision to dosage adjustment by preventing the oxidative damage, thereby preserving renal function using male albino rats (Heeba and Mahmoud, 2016).

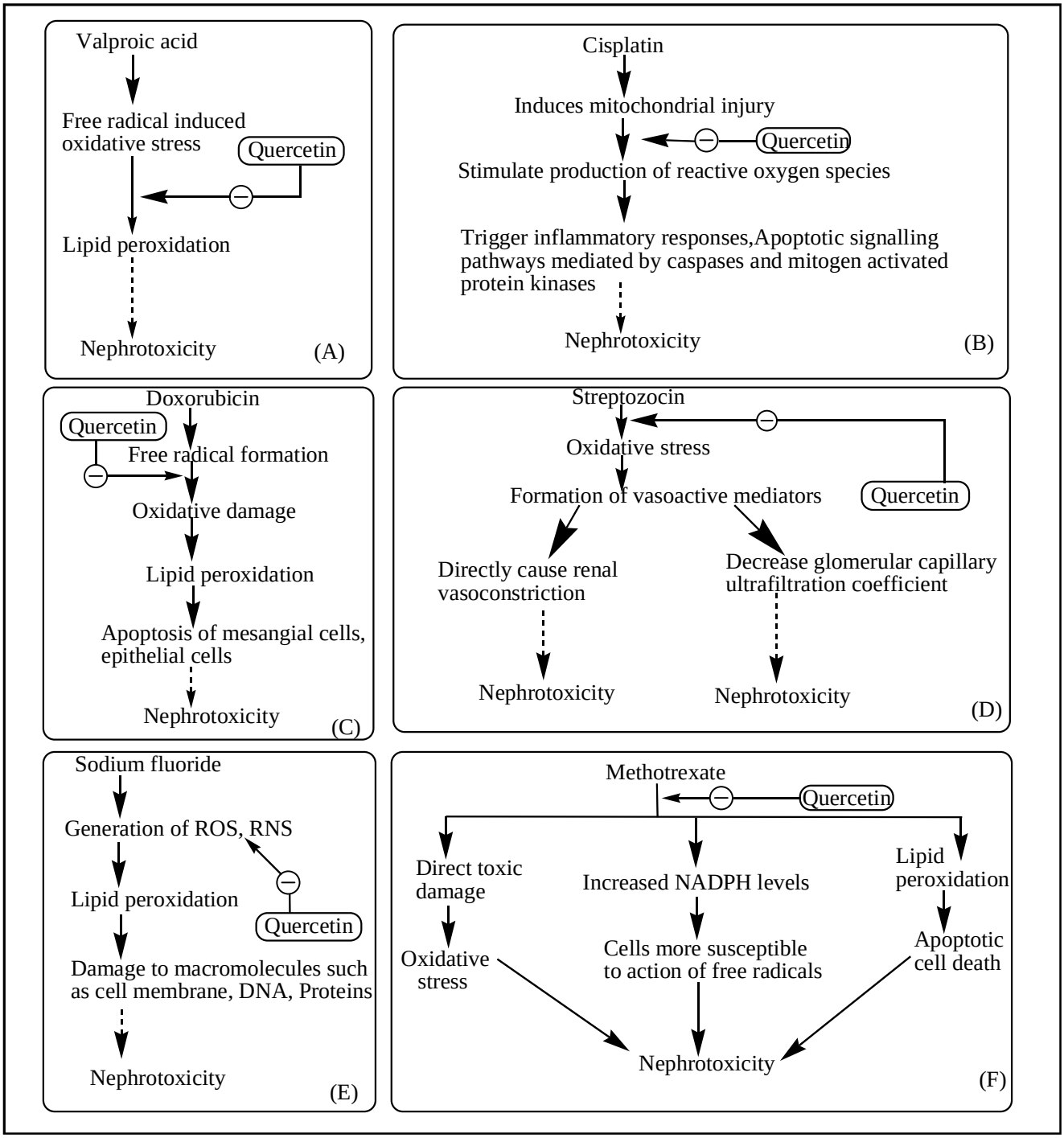

Figure 1: Mechanism involved in the nephroprotective activity of quercetin against valproic acid (A), cisplatin (B), doxorubicin (C), streptozocin (D), sodium fluoride (E) and methotrexate (F).

Table 1: Nephroprotective effects of quercetin

Nephrotoxicant, dose	Animal model/tissue used	Quercetin dose	Effector mechanisms	References
Valproic acid (20 mg)	Male wistar rats 3-4 weeks old, 100-200 gm	0.05 mM	Oxidative stress lipid peroxidation	Chaudhary *et al*., 2015
Cisplatin (4 mg/kg, i.p.)	Breast adenocarcinoma cells in male fischer rats	50 mg/kg/day i.p.	Lipid peroxidation expression of inflammatory markers	Sanchez-Gonzalez *et al*., 2011
Doxorubicin (15 mg/kg at 7 day of experiment i.p.)	Male albino rats	10, 50, 100 mg/kg orally	Lipid peroxidation increased BUN and NO levels	Heeba and Mahmoud, 2016
Streptozotocin (45 mg/kg IV)	Sprague dawley diabetic rats	10 mg/kg/day orally	Oxidative stress increased proteinuria, polyuria, serum creatinine	Anjaneyulu and Chopara, 2004
Sodium fluoride 600 ppm	Male wistar rats	20 mg/kg i.p.	Oxidative stress induced renal injury	Nabavi *et al*., 2012
Methotrexate 20 mg/kgi.p	Male rats	15 mg/kg IV	Tubular degeneration and dilation	Erboga *et al*., 2015
Lead acetate 500 mg Pb/l	Adult male wistar rats	25,50 mg/kg intragastrically	Oxidative stress inflamation	Liu *et al*., 2012
Cadmium 5 mg/kg oral	Male albino rats	50 mg/kg oral	Oxidative stress tubular necrosis degeneration	Renugadevi and Prabu, 2010
Lindane 100 mg/kg dissolved in olive oil	Female albino wistar rats	10 mg/kg oral oxidative stress	Free radical generation	Padma *et al*., 2012
0.75% adenine diet	Adult male wistar rats	25 mg/kg/day	Vascular calcification oxidative stress	Chang *et al*., 2017
Cisplatin 8 mg/kg i.p.	Male wistar rats	50 mg/kg i.p.	Oxidative stress structural damage	Ilic *et al*., 2016
PCM-650 mg/kg PO	Male wistar rats	20 mg/kg PO	Oxidative stress	Yousef *et al*., 2010
Gallium arsenide 20 mg/kg orally	Male albino rats	25 mg/kg alternative days orally	Generation of ROS	Bhatt and Flora, 2009
Chlorpyrifos 5.4 mg/kg oral gavage	Male wistar rats	20 mg/kg,gavage	Oxidative stress	Kalender *et al*., 2012
Tio_2 5 mg/kg I.V.	Male wistar rats	5 mg/kg/day,i.p	Oxidative stress	Gonzalez-Esquivel *et al*., 2015
Ferric nitrile triacetate 8 mg iron /kg i.p.	Mice	2 mg/kg I.P. 30 min before Fe-NTA administration	Acute proximal tubular necrosis lipid peroxidation oxidative stress	Singh *et al*., 2004
Dichlorvas 7.2 mg/kg	Male wistar rats	2, 10, 50 mg/kg intragastrically	Renal tubular injury decreased glomerular filtrationoxidative stress	Hou *et al*., 2014
Melphalan 0.2 mg/kg for 7 days	Male wistar rats	20 mg/kg for 7 days	Lipid peroxidation	Olayinka *et al*., 2014
APAP 3 gm/kg oral	Sprague dawley rats	15 mg/kg/day orally	Oxidative and nitrosative stress	El-Shafey *et al*., 2015
Mercury chloride 20 mg/kg orally single dose	Male sprague-dawley rats	250 mg/kg orally	Proximal tubular damage	Shin *et al*., 2015
Ischemia/reperfusion	Male sprague-dawley rats	2,30 mg/kg I. P.	Renal ischemia due to arterial occlusion, Renal cell death renal failure	Singh *et al*., 2004

Gentamycin 100 mg/kg bw/day I. P diclofenac 5 mg/kg b wt /day	Male albino rats	2 mg/kg b. wt taurine 0.75g/kg b. wt	Enhance ROS renal cortical Na+, K+ATPase depressionelevations in serum urea, creatinine and urinary N-acetyl-b-D-glucosaminidase (NAG) tubular renal damage	Eldin *et al*., 2008
Ammonium fluoride 2 my F/m^3	Male wistar rats	7 mg F/kg	Oxidative stress	Juzyszyn *et al*., 2002
Snake venom 3.84 mg/kg, ip	Albino rats	30 micrometer/ kg ip	Increased levels of creatinine.	Al Asmari *et al*., 2016
Gentamycin 80 mg/kg /d ip	Female albino wistar rats	50 mg/kg day	Increase in TBARS oxidative stress damage	Abdel-Raheem *et al*., 2009
Arsenite 25 ppm	Mouse	0.2 mmol, orally	Increase TBARS	Mishra and Flora, 2008
Atrazine 120 mg /kg	Male albino wistar	5 or 10 mg /kg	Lipid per oxidation oxidative stress	Abarikwu *et al*., 2016
Ionising radiation (8-Gy whole-abdominal IR)	Sprague-dawley rats	20 mg/kg, ip	Reactive oxygen species generated by radiolytic hydrolysis	Ozyurt *et al*., 2014
Iron (500 mg/kg in form of iron dextran)	Mice	1% w/w	Oxidative injury	Zhang *et al*., 2011

2.4 Protective activity against streptozotocin (STZ)-induced diabetic nephropathy

STZ is an alkylating antineoplastic agent. It induces nephrotoxicity by directly causing vasoconstriction due to formation of vasoactive mediators by oxidative stress (Figure 1D). A study has demonstrated the nephroprotective action of QR (10 mg/kg per day, PO) against STZ (45 mg/kg, IV) by antioxidative mechanism using Sprague-dawley rats (Anjaneyulu and Chopra, 2004).

2.5 Protective activity against sodium fluoride (NaF)-induced nephrotoxicity

NaF is used in minute amounts for the fluoridation of drinking water, toothpaste, *etc*. It induces generation of ROS and reactive nitrogen species and causes LPO, damage to macromolecules such as cell membrane, DNA, proteins resulting nephrotoxicity (Figure 1E). A study has shown the nephroprotective effect of QR (20 mg/kg, IP) against NaF-induced nephrotoxicity (600 ppm, PO) by antioxidant mechanism using male wistar rats (Nabavi *et al*., 2012).

2.6 Protective activity against methotrexate (MTX)-induced nephrotoxicity

MTX is a folate antagonist and induces nephrotoxicity by causing direct toxic damage, increased NADPH levels and lipid peroxidation (Figure 1F). A study has shown that QR (15 mg/kg, IV) has protective activity against MTX (20 mg/kg, IP) induced hepatotoxicity by antioxidant defensive mechanism using rats (Erboga *et al*., 2015).

2.7 Protective activity against lead (Pb)-induced nephrotoxicity

Pb induces ROS and subsequent inflammation by activating mitogen activated protein kinase (MAPK) and resulting in nephrotoxicity (Figure 2G). A study has demonstrated that QR (25 and 50 mg/kg intragastrically once daily) in diets exerts the nephroprotective effects against lead acetate (500 mg Pb/l, PO) by inhibition of Pb induced kidney inflammation using wistar rats (Liu *et al*., 2012).

2.8 Protective activity against cadmium (Cd)-induced nephrotoxicity

Cd forms a complex with cysteine rich protein and induces oxidative stress and LPO resulting in nephrotoxicity (Figure 2 H). A study has shown that QR (50 mg/kg, PO) might have protective effect against Cd induced nephrotoxicity (5 mg/kg, PO) by antioxidant mechanism using albino rats (Renugadevi *et al*., 2010).

2.9 Protective activity against lindane (LN)-induced nephrotoxicity

Lindane is an organochlorine insecticide that has been used as a pediculicide and a scabicide. LN dissolved in olive oil induces cell damage by generating free radicals (Figure 2I). The study has shown that QR (10 mg/kg in 50% ethanol) has nephroprotective activity against LN (100 mg/kg) by inhibiting the oxidative stress in rat model (Padma *et al*., 2012).

2.10 Protective activity against adenine (AD)-induced nephrotoxicity

AD forms crystals during renal excretion and induces tubule interstitial fibrosis resulting in inflammation (Figure 2J). A study showed that the QR (25 mg/kg, PO) has nephroprotective activity against AD (0.75% AD diet gavage) by the modulation of oxidative stress and iNOs/p38 MAPK pathway in male wistar rats (Chang *et al*., 2017).

2.11 Protective activity against cisplatin (CS)-induced nephrotoxicity

CS is an antioneoplastic drug with serious side effects such as nephrotoxicity. It causes acute kidney injury through glomerular congestion (Figure 2K). A study has demonstrated the possible beneficial effect of QR (50 mg/kg, IP) on CS induced nephrotoxicity (8 mg/kg, IP) by decreasing level of oxidative stress in male wistar rats (Ilic *et al*., 2016).

2.12 Protective activity against paracetamol (PCM)-induced nephrotoxicity

PCM is used as analgesic and antipyretic agent and the over dose causes PCM-induced toxicity. PCM causes elevation of TBARS, decreases the renal blood flow and damages the proximal tubule thus causing acute or chronic renal toxicity (Figure 2M). A study has shown the potential protective role of QR (20 mg/kg, PO) against PCM-induced nephrotoxicity (650 mg/kg, PO) by mitigating the rise in TBARS and restoring the activities of antioxidant enzymes using male wistar rats (Yousef *et al*., 2010).

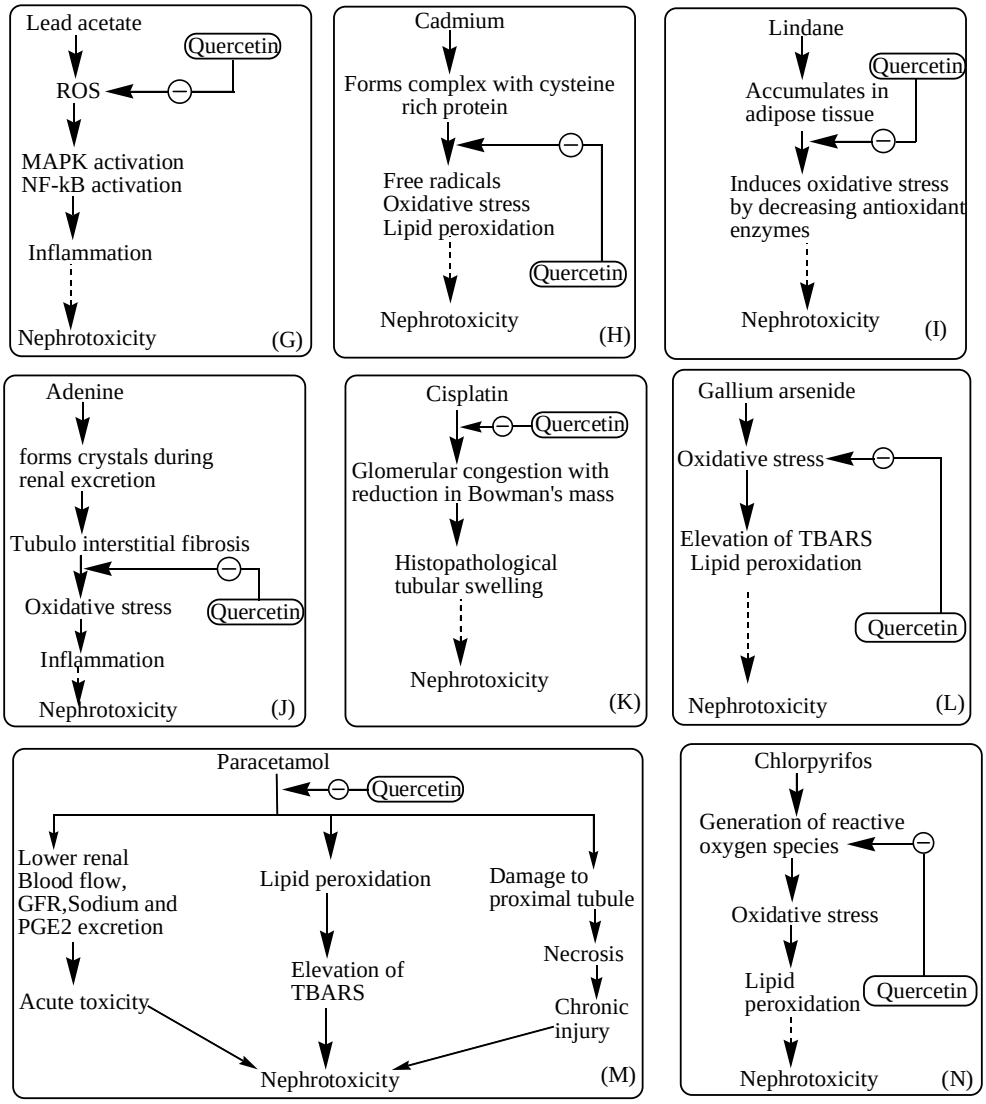

Figure 2: Mechanisms involved in the nephroprotective activity of quercetin against lead acetate (Cr), cadmium (H), lindane (I), adenine (J), cisplatin (K), gallium arsenide (L), paracetamol (M), and chlorpyrifos (N).

2.13 Protective activity against gallium arsenide (GaAs)-induced nephrotoxicity

GaAs an inter-metallic semiconductor and it produces ROS and decreases the levels of antioxidant system and causes nephrotoxicity (Figure 2L). A study conducted has showed that QR (25 mg/kg orally) has nephroprotective activity against the GaAs (25 mg/kg) by inhibiting the oxidative stress in male albino rats (Bhatt *et al*., 2009).

2.14 Protective activity against chlorpyrifos (CPF)-induced nephrotoxicity

CPF modify endogeneous antioxidants, thus causes renal damage (Figure 2N). A study showed that QR (20 mg/kg, PO) has nephroprotective activity against the CPF (5.4 mg/kg, 1/25 of the oral LD50, PO) by inhibiting the oxidative stress in *in vivo* model (Kalender *et al*., 2012).

2.15 Protective activity against TiO_2-induced nephrotoxicity

TiO_2 nanoparticles can cause oxidative stress in liver and kidney (Figure 3O). A study showed that QR (5 mg/kg/day, IP) has nephroprotective activity against the TiO_2 (5 mg /kg, IV) by inhibiting the oxidative damage in male wistar rats (Gonzalez-Esquivel *et al*., 2015).

2.16 Protective activity against ferric nitrilotriacetate (Fe-NTA)-induced nephrotoxicity

An iron chelate, Fe-NTA, induces acute proximal tubular necrosis as a consequence of lipid peroxidation and oxidative tissue damage that eventually leads to high incidence of renal adenocarcinomas in rodents (Figure 3P). A study has demonstrated that QR (2 mg/kg, IP) has protective activity against Fe-NTA-induced nephrotoxicity (8 mg iron/kg, IP) by antioxidant mechanism in rats (Singh *et al*., 2005).

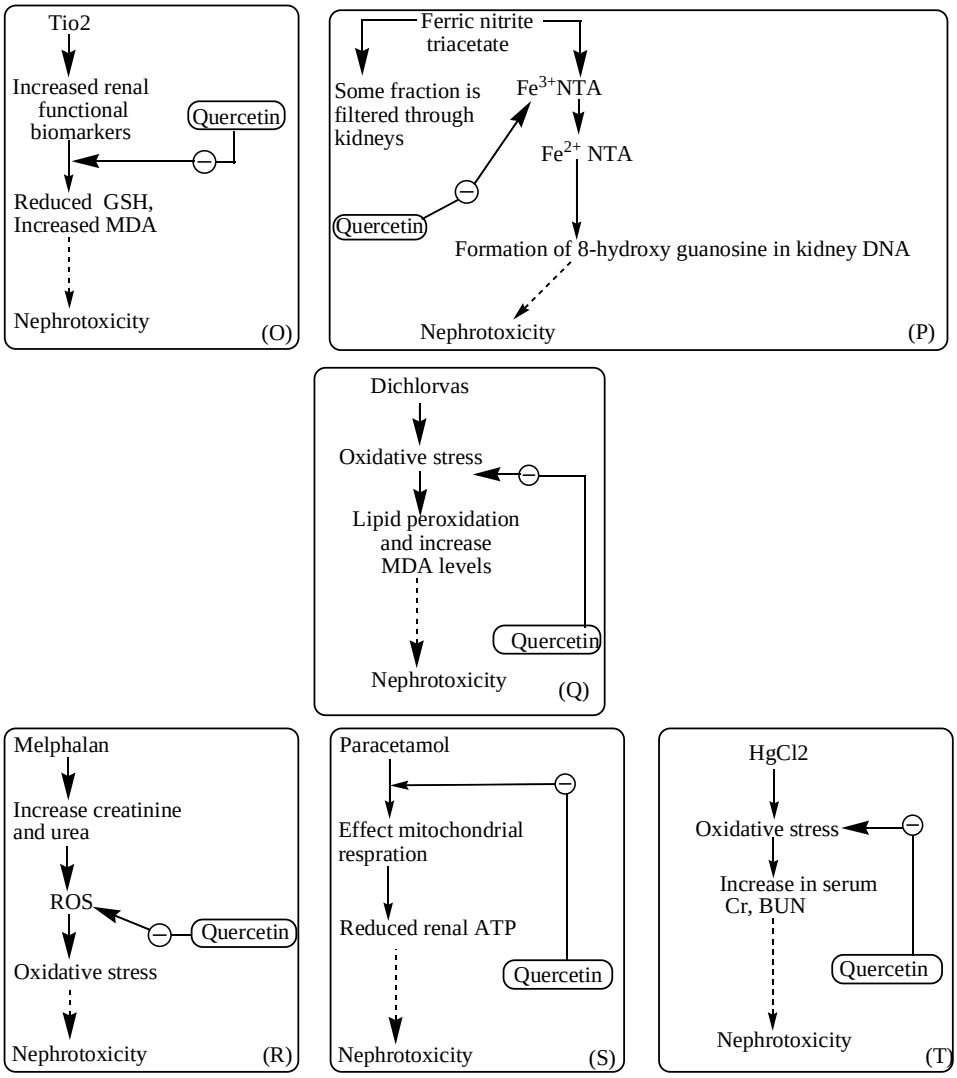

Figure 3: Mechanisms involved in the nephroprotective activity of quercetin against TiO2(O), ferric nitrite triacetate (P), dichlorvas (Q), melphalan (R), paracetamol (S) and $HgC1_2$ (T) .

2.17 Protective activity against dichlorvos (DDVP)-induced nephrotoxicity

DDVP is an organophosphorus insecticide, DDVP induces ROS, thus causing lipid peroxidation and finally leading to nephrotoxicity (Figure 3Q). A study showed that the QR (50 mg/kg, PO) has nephroprotective activity against DDVP (7.2 mg/kg) by inhibiting oxidative stress in rats (Hou *et al*., 2014).

2.18 Protective activity against melphalan (MPLN)-induced nephrotoxicity

MPLN is an alkylating agent used to treat different kinds of cancers such as melanoma, ovarian cancer, multiple myeloma. But, it increases the levels of urea and creatinine and finally causes renal damage (Figure 3R). A study demonstrated that quercetin (20 mg/kg) has shown nephroprotective and also hepatoprotective activity against MPLN (0.2 mg/kg). When MPLN is pre or co-treatment with QR, it (QR) ameliorated the levels of renal function indices by acting on reactive oxygen species and hepatic ascorbic acid and GSH and activities of GST, SOD, and CAT were also decreased using *in vivo* model (Olayinka *et al*., 2014).

2.19 Protective activity against PCM-induced nephrotoxicity

PCM causes nephrotoxicity by an enzyme CYP 450 that produces the metabolite known as NAPQI that binds to cellular proteins that

induces the oxidative stress and mitochondrial dysfunction and leads to increases the TBARS and decreases GSH and causes cellular death of the kidney and finally leads to nephrotoxicity. High doses of PCM can cause life-threatening hepatic and renal dysfunction by effecting mitochondrial respiration (Figure 3S). A study showed that QR (15 mg/kg/day) supplementation prior to the high single oral dose of PCM (3 g/kg) has protective effects on the kidneys by decreasing the effect of PCM on mitochondrial respiration, and thereby increasing the renal ATP in sprague-dawley rats (El Shafey *et al*., 2015).

2.20 Protective activity against mercury chloride ($HgCl_2$)-induced nephrotoxicity

$HgCl_2$ is used as an antiseptic and disinfectant. $HgCl_2$ causes nephrotoxicity by inducing the oxidative stress results in increased urine volume, and decrease the urine pH and blood urea nitrogen and serum creatinine finally leads to renal tissue damage (Figure 3T). A study showed that QR (250 mg/kg, PO) has nephroprotective activity against $HgCl_2$ by decreasing the accumulation of $HgCl_2$ in the kidney in sprague-dawley male rats (Shin *et al*., 2015).

2.21 Protective activity against ischemia/reperfusion-induced nephrotoxicity

The common cause of nephrotoxicity is renal ischemia as a result of shock, arterial occlusion and organ transplantation. I/R causes nephrotoxicity by induces the TBARS, Protein carbonyl content, TNF-a and decreases the GSH, CAT and SOD and finally leads to death of renal tissue (Figure 4U). In the pathogenesis of I/R induced renal toxicity, reactive oxygen radicals play an important role. A study showed that QR (2 mg/kg, 30 mg/kg, IP) has its renal protective activity against the damage imposed by ROS during renal I/R by reducing elevated levels of TBARS and restoring renal antioxidant enzymes in *in vivo* model (Singh *et al*., 2004).

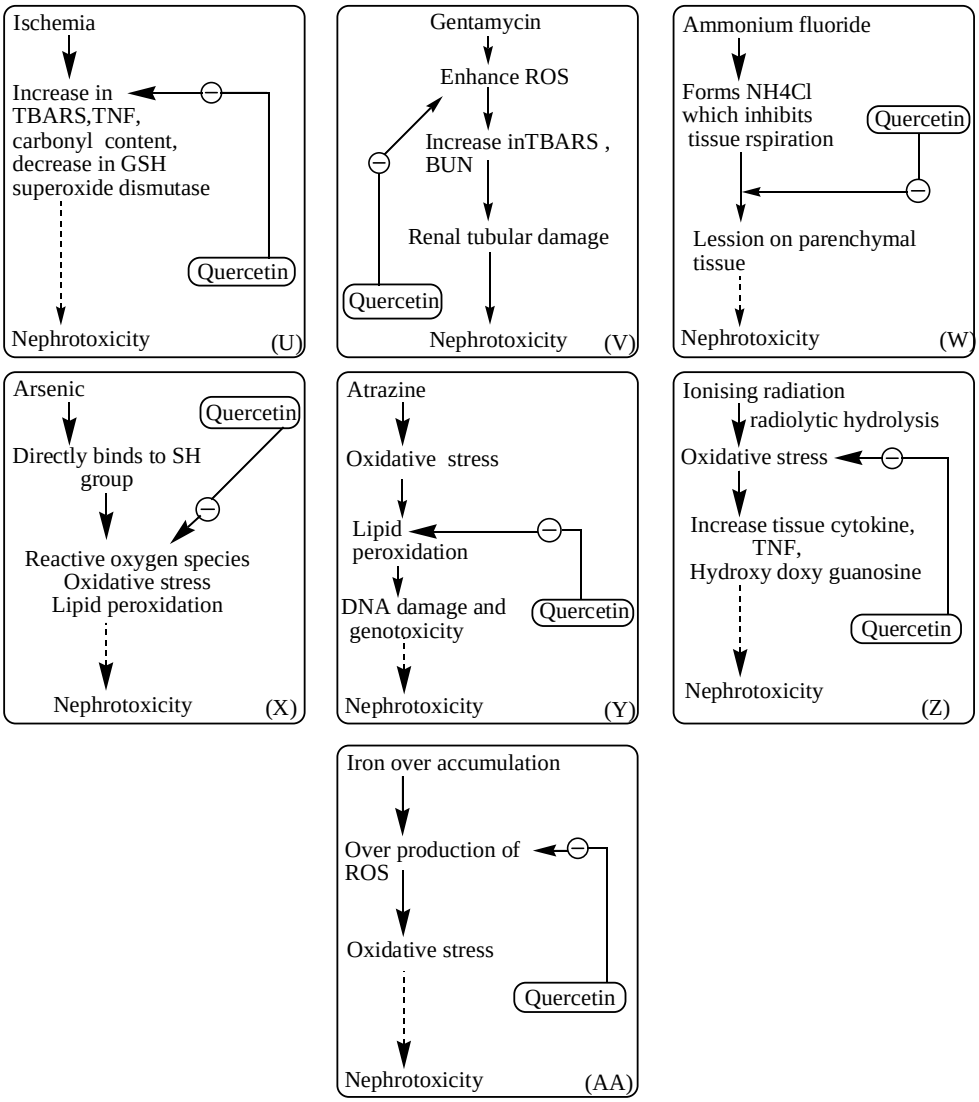

Figure 4: Mechanisms involved in the nephroprotective activity of quercetin against ischemia (U), gentamycin (V), ammonium fluoride (W), arsenic (X), atrazine (Y), ionising radiation (Z) and iron (AA).

2.22 Protective activity against gentamycin (GM) and diclofenac (DC)-induced nephrotoxicity

GM belongs to aminoglycoside antibiotics used in the management of several bacterial infections including conjunctivitis. GM causes nephrotoxicity by enhancing the ROS and leads to decreases GSH, SOD, CAT activities and increase TBARS, BUN and SC and causes tubular renal damage or degenerative changes in glomeruli and tubules and finally leads to nephrotoxicity (Figure 4V). A study justified that QR had as nephroprotective activity against the nephrotoxicity caused by GM (100 mg/kg, IP for 8 days), DC (5 mg/kg/day for 28) days due to its activity against reactive oxygen species in rats (Eldin *et al*., 2008).

2.23 Protective activity against ammonium fluoride (NH_4F)-induced nephrotoxicity

NH_4F is an inorganic compound and it is used in preserving wood, antiseptic in brewing of beer in cleaning products used in the home, laundry detergents, soaps, printing and dying industry. NH_4F forms NH_4Cl which inhibits tissue respiration and forms lesions on the parenchymal tissue ultimately leading to nephrotoxicity (Figure 4W). A study showed that mixture containing 1:1 quercetin 5', 8-disulfonic (Na_2QDSA) and monosulfonic acid sodium salts (NaQSA-5'/NaQSA-8) as chewing pellets (7 mg F/kg) showed nephro-protective activity against NH_4F (2 mg F/m^3, inhalation) by inhibiting the formation of NH_4Cl in male wistar rats (Juzyszyn *et al*., 2002).

2.24 Protective activity against snake venom-induced nephrotoxicity

Snake venom significantly increases the creatinine and causes histopathological damage of the tissue architecture. A study showed that QR (30 mM/kg, IP) has renoprotective action against sub-lethal venom (3.84 mg/kg, IP) doses of echiscoloratus (Ec) viper snake by modulating the biochemical parameters and histological damage and is attributed to the potential protective effects in albino rats (Al Asmari *et al*., 2016).

2.25 Protective activity against GM-induced nephrotoxicity

GM belongs to the class of aminoglycoside antibiotics used in the treatment of several bacterial infections including conjunctivitis. GM causes nephrotoxivity by enhances the ROS and leads to decreases GSH, SOD, CAT activities and increase TBARS, BUN and SC and causes tubular renal damage or degenerative changes in glomeruli and tubules and finally leads to nephrotoxicity (Figure 4V). A study showed that QR (50 mg/kg/d) for 7 days had as renoprotective activity against the nephrotoxicity caused by GM (80 mg/kg/d, IP) for 7 days by significantly decreasing GSH levels, SOD, CAT activities and increase in TBARS levels in rats (Abdel-Raheem *et al*., 2009).

2.26 Protective activity against arsenite-induced nephrotoxicity

Arsenic causes nephrotoxicity by directly binding to SH groups and indirectly through generation of ROS and leads to decreases blood delta-amino levulinic acid dehydratase, GSH and increases platelet and TBARS (Figure 4X). A study showed that QR (0.2 mmol, orally) has nephroprotective action against arsenite (25 ppm as sodium arsenite in drinking water) by minimizing lipid peroxidation and decreasing the ROS in *in vivo* model (Mishra *et al*., 2008).

2.27 Protective activity against atrazine (ATZ)-induced nephrotoxicity

ATZ is an herbicide which is a member of triazine chemical class. ATZ causes nephrotoxicity by inducing oxidative stress and increasing the lipid peroxidation, CAT, SOD, GSH and MDA which leads to DNA damage and genotoxicity in kidneys, stomach and liver (Figure 4Y). A study showed that QR (10 mg/kg, PO) has nephroprotective action against ATZ (120 mg/kg, PO) by inhibiting the lipid peroxidation, and thereby decreasing nephrotoxicity in adult male albino wistar rats (Abarikwu *et al*., 2014).

2.28 Protective activity against ionizing radiation-induced nephrotoxicity

Ionizing radiation (IR) can cause cell death through the ROS generated by radiolytic hydrolysis and leads to the increase tissue cytokine, TNF-a, capase 3 and myeloperoxidase and leads to DNA damage, tissue 8 hydroxy deoxyguanosine and causes neutrophil infiltration and apoptosis (Figure 4Z). A study showed that QR (20 mg/kg, IP) has renoprotective activity against IR by its free radical scavenging and antioxidant properties, attenuates IR-induced oxidative renal injury in sprague-dawley rats (Ozyurt *et al*., 2014).

2.29 Protective activity against iron-induced nephrotoxicity

FE is an essential element used for the production of heme, a protein for production of red blood cells. But, excessive accumulation of Fe in the body leads to organ damage. Fe causes toxicity due to over accumulation leads to the over production of reactive oxygen species that leads to increases the production of TBARS, BUN and SC and decreases the SOD, CAT, GSH production leads to the tubular renal damage or degenerative changes in glomeruli and tubules and causes nephrotoxicity (Figure 4AA). A study showed that QR (1% w/w) has nephroprotective activity against Fe (500 mg/kg) by inhibiting the over production of carbony content, ROS thus decreasing the oxidative stress as the flavonoids contain high affinity to FE in *in vitro* model (Zhang *et al*., 2011).

3. Conclusion

The current review explained the nephroprotective activities of QR against various drug and chemicals-induced nephrotoxicity due to its antioxidant, free radical-scavenging, anti-inflammatory, anti-apoptotic mechanisms. This will help the scientific community to reduce the nephrotoxicity using quercetin.

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Conflicts of interest

The authors declare no conflicts of interest relevant to this article.

Abbreviations

AD, Adenine; AKI, Acute Kidney Injury; ALP, Alkaline Phosphatase; ATZ, Atrazine; BUN, Blood Urea Nitrogen; CAT, Catalase; Cd, Cadmium; CdF2, Cadmium Fluoride; COX-2, Cyclooxygenase-2; CPF, Chlorpyrifos; CS, Cisplatin; DDVP, Dichlorvos; DC, Diclofenac; DOX, Doxorubicin; ERK, Extracellular-Receptor Kinase; Fe, Iron; Fe-NTA, Ferric Nitrilotriacetate; GaAs, Gallium Arsenide; GM, Gentamycin; GPx, Glutathione Peroxidise; GR, Glutathione

Reductase; GSH, Reduced Glutathione; GSSG, Oxidized Glutathione; GST, Glutathione-S-transferase; Hg, Mercury; $HgCl_2$, Mercury Chloride; IL, Interleukin; iNOS, Inducible Nitric Oxide Synthase; IR, Ionizing Radiation; I/R, Ischemia / Permission; JNK, c-Jun N-terminal Kinase; LPO, Lipid Peroxidation; LN, Lindane; MAPK, Mitogen Activated Protein Kinase; MDA, Malondialdehyde; MPLN, Melphalan; MTX, Methotrexate; NAC, N-acetylcysteine; NaF, Sodium Fluoride; NF-kB, Nuclearfactor-kB; NH_4F, Ammonium Fluoride; OP, Organophosphate; PCM, Paracetamol; Pb, Lead; QR, Quercetin; ROS, Reactive Oxygen Species; SC, Serum Creatinine; SOD, Superoxide Dismutase; STZ, Streptazotocin; TBARS, Thiobarbituric Acid Reactive Substances; TNF-a, Tumour Necrosis Factor-a; UA, Uric Acid; VPA, Valproic Acid.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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